Clinical Research

PROCEEDINGS

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Atlantic City, April 1956

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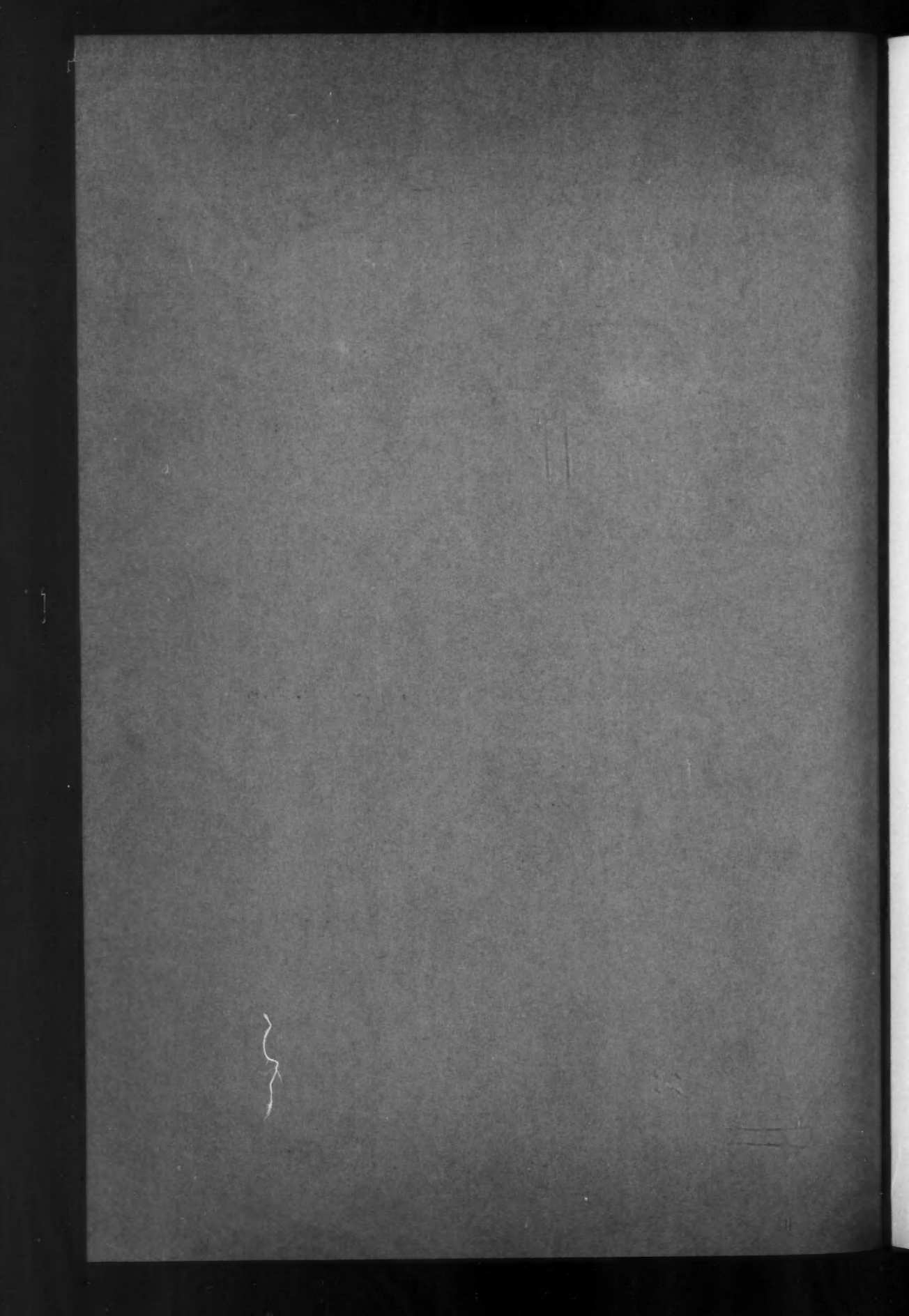

PROGRAM

National Meeting

American Federation for Clinical Research

Sunday, April 29, 1956

Steel Pier Theater, Atlantic City, New Jersey

Dr. Carleton B. Chapman, Presiding

Presentations will be limited to ten minutes; five minutes will be allowed for discussion.

MORNING SESSION

9:00–9:15—Business Meeting

1. **Alterations in Cerebral Circulation and Function in Cheyne-Stokes Respiration**
   Herbert O. Sieker, Herbert R. Karp and Albert Heyman.* Duke University School of Medicine and the V. A. Hospital, Durham. ***page 154***

2. **The Hemodynamic Effects of Quinidine in Dogs**
   George G. Rowe, Dean A. Emanuel, George M. Maxwell,* John F. Brown,* Cesar Castillo Alzamora,* Benjamin Schuster,* Q. R. Murphy* and Charles W. Crumpton.* University of Wisconsin School of Medicine, Madison. ***page 104***

3. **The Hematocrit of the Human Forearm Capillary Bed**
   Lawrence S. Lilienfield, Renato D. Kovach, Frank A. Perfido,* and Edward D. Freis.* Georgetown University Medical Center and the V. A. Hospital, Washington, D. C. ***page 110***

4. **Simultaneous Estimation of Plasma Volume with Evans Blue Dye and I^{131}-labeled Globulin**
   Gerald P. Rodnan. University of Pittsburgh School of Medicine, Pittsburgh. ***page 90***

5. **Correlation of Clinical and Hemodynamic Studies in Patients with Thyroid Disease**
   John S. Graettinger, J. J. Muenster, C. S. Checchia* and J. A. Campbell.** University of Illinois College of Medicine, Chicago. ***page 120***

6. **Hemodynamic Studies in the Pulmonary and Peripheral Circulation during Acute Hypoventilation**
   A. Buhlmann, G. Hossli and P. Luchsinger (introduced by *Georges F. McCormick*). University Hospital, Zurich, Switzerland. ***page 153***

7. **Venous-Arterial Admixture in Polycythemia and Pulmonary Emphysema**
   James P. Lillehei, Robert L. Johnson, Jr.,* Nancy Wu,* E. Richard Halden* and Carleton B. Chapman.* University of Texas Southwestern Medical School, Dallas. ***page 152***

8. **A Rational Therapy of Systemic Lupus Erythematosus**
   N. B. Kurnick. University of California at Los Angeles School of Medicine and the Veterans Administration Hospital, Long Beach. ***page 77***

9. **Observations in a "Control" Group of Patients in Psychosomatic Investigation**
   *Solomon Papper and Juanita Handy.** Boston University and Tufts University Schools of Medicine and the V. A. Hospital, Boston. ***page 114***

10. **Serial Renal Biopsies and Function in Acute Glomerulonephritis**
    *Alvin E. Parrish and John S. Howe.** George Washington University and the V. A. Hospital, Washington, D.C. ***page 139***

11. **A Quantitative Estimate of Net Splanchnic Ketone Production following Insulin Hypoglycemia in Man**
    Harry T. McPherson, Emile E. Werk, Jr.,* Frank L. Engel* and Jack D. Myers.* Duke University School of Medicine, Durham. ***page 122***

12. **Physiologic Action of a New Oral Hypoglycemic Agent**
    John A. Moorhouse and Robert M. Kark.* University of Illinois College of Medicine, Chicago ***page 124***

13. **The Prevention of Hyperglycemia by Potassium Administration**
    Nancy Nichols. Harvard Medical School, Boston. ***page 122***

14. **Alterations in Serum Glutamic Oxalacetic Transaminase (SGO-T), Serum Glutamic Pyruvic Transaminase (SGP-T) and Lactic Dehydrogenase (LD) following Experimental Myocardial Infarction**
    Paul Ruegsegger, Irwin Nydick, Felix Wroblewski and John S. LaDue.* Cornell University Medical College (Sloan-Kettering Division) and Memorial Center for Cancer and Allied Diseases, New York. ***page 101***

* By invitation

AFTERNOON SESSION

1:45–2:00—Business Meeting
2:00—Presidential Address

15. **Studies of the Relationship between Structure and Function of Steroids: The 2-Methyl-Corticosteroids**
Grant W. Liddle, June E. Richard and Gordon M. Tomkins.** National Heart Institute and National Institute of Arthritis and Metabolic Diseases, Bethesda. *page 125*

16. **Studies in Cholesterol Degradation**
Marvin D. Siperstein (introduced by *Donald W. Seldin*). University of Texas Southwestern Medical School, Dallas. *page 129*

17. **Renal Arteriovenous Ammonium Difference and Total Renal Ammonium Production in Normal, Acidotic and Alkalotic Dogs**
J. William Poppell, F. Cuajunco, Jr.,* J. S. Horsley, III,* H. T. Randall* and Kathleen E. Roberts.* Memorial Center for Cancer and Allied Diseases, New York. *page 137*

18. **Water and Solute Excretion in Pitressin-Resistant Diabetes Insipidus**
Jack Orloff and Mackenzie Walser. National Heart Institute, Bethesda. *page 136*

19. **Sequelae of Prednisone Treatment of Acute Rheumatic Fever**
*Richard T. Smith and Robert A. Good.** University of Minnesota Medical School, Minneapolis. *page 156*

20. **The Measurement of Erythrocyte Survival with P^{32}-tagged Diisopropylfluorophosphonate (DPF^{32})**
Klaus Mayer and Allyn B. Ley.* Memorial Center for Cancer and Allied Diseases, New York. *page 80*

21. **A Simple Method for Measurement of Erythropoiesis in Man**
Arthur J. Samuels, Lyle Reinhardt, Bohdan Jelinek* and Dorli Furrer.** Hospital for Tumors and Allied Diseases and Medical Research Center, City of Hope Medical Center, Duarte, California. *page 77*

22. **The Relation of Neoplastic Tissue Antigens to "Autoimmune" Hematologic Syndromes**
*Mario Stefanini, Sergio I. Magalini and James H. Patterson.** Tufts University School of Medicine, Boston. *page 82*

23. **Properdin Levels in Human Disease**
*Carl F. Hinz, Jr. and John R. Murphy.** Western Reserve University School of Medicine, Cleveland. *page 93*

24. **Control of Blood Ammonia in Cirrhosis by Oral Neomycin**
Curtis J. Fisher, and William W. Faloon.* State University of New York, Upstate Medical Center, Syracuse. *page 147*

25. **Alkali Therapy for Postsympathectomy Postural Hypotension in the Presence of Mild Acidosis**
F. J. Haddy, F. W. Wokalek and L. T. Minish, Jr. The Norton Infirmary, Louisville. *page 109*

26. **The Natural History of Hypertensive Retinopathy as Revealed by Serial Color Photographs**
Albert A. Brust (introduced by *Joseph S. Wilson*). Emory University School of Medicine, Atlanta. *page 107*

SUBSECTION PROGRAMS

Subsection on Cardiovascular Disease

Rutland Room, Haddon Hall, 8 p.m., Sunday, April 29, 1956

S. Gilbert Blount, *Chairman, Presiding*

1. **Anaerobic Metabolism of the Myocardium and Other Organs during Exercise and Hypoxia**
   William E. Huckabee. Boston University School of Medicine, Boston Massachusetts
   page 100
2. **The Effect of Cigarette Smoking on Coronary Flow and Myocardial Metabolism in Man**
   L. M. Bargeron, F. Gonlubol,* D. Ehmke* and A. Calix** (introduced by *R. J. Bing*). Medical College of Alabama, Birmingham.
   page 100
3. **Effect of Mild Steady-State Exercise on Pulmonary Vascular Resistance of Normal Subjects and Those with Compensated and Decompensated Aortic Valvular Lesions**
   Salvatore M. Sancetta and Jerome Kleinerman. Western Reserve University School of Medicine, Cleveland.
   page 151
4. **Left Heart Catheterization in Aortic Stenosis**
   Paul Novack, Leonard A. Cobb,* Hiroshi Kuida,* Florence W. Haynes* and Lewis Dexter.* Peter Bent Brigham Hospital and Harvard Medical School, Boston.
   page 97
5. **The Hemodynamic Diagnosis of Tricuspid Stenosis**
   Thomas Killip, III and Daniel S. Lukas.* New York Hospital-Cornell Medical Center, New York.
   page 98

Joint Meeting
Subsection on Gastroenterology
and the Gastroenterology Research Group

Viking Room, Haddon Hall, 8 p.m., Sunday, April 29, 1956

E. Clinton Texter, Jr., *Chairman, Presiding*

PROBLEMS OF INTESTINAL ABSORPTION

Part I. PHYSIOLOGY: METHODS OF STUDY. *Moderator*, Joseph B. Kirsner, University of Chicago, Chicago.

Isotopic Technics. *R. J. Reitemeier.* Mayo Clinic, Rochester, Minnesota.

Absorption Technics, including Labeled Fat. *Perry J. Culver.* Harvard Medical School, Boston.

Balance Technics. *M. W. Comfort.* Mayo Clinic, Rochester, Minnesota.

General Discussion

Brief Intermission

Part II. PATHOPHYSIOLOGY OF MALABSORPTION SYNDROMES. *Moderator*, Thomas P. Almy, Cornell University, New York.

Application of Newer Methods of Studying Intestinal Absorption to Sprue and Other Conditions. *J. M. Ruffin.* Duke University, Durham.

Malabsorption Syndromes in the Postoperative Patient. *E. H. Ellison.* Ohio State University, Columbus.

General Discussion

Part III. RECENT STUDIES ON INTESTINAL ABSORPTION

Blood Carotene and Steatorrhea
Julius Wenger (introduced by *E. C. Texter, Jr.*). University of Chicago, Chicago.
page 133

Effect of Carbohydrate Ingestion on Postprandial Lipemia
*Margaret J. Albrink and Evelyn B. Man.** Yale University, New Haven.
page 121

Effect of a Hypertonic Solution on Intestinal Absorption
Thomas R. Hendrix (introduced by *Kerrison Juniper, Jr.*). Evans Memorial, Massachusetts Memorial Hospitals, and Department of Medicine, Boston University, Boston.
page 132

Subsection on Medical Education

Music Room, Haddon Hall, 8 p.m., Sunday, April 29, 1956

John P. Colmore, *Chairman, Presiding*

1. **Conference and Panel Teaching in the Medical Curriculum as a Form of Interdepartmental Teaching, with Special Comments on the Teaching of Therapy**
   Daniel H. Labby. Portland, Oregon. ***page 115***
2. **A Pattern for Instruction in Occupational Medicine**
   *Jean Spencer Felton** (introduced by *Stewart Wolf*). Oklahoma City, Oklahoma. ***page 116***
3. **Improving Teaching on Ambulant Patients**
   *Kerr L. White and William L. Fleming** (introduced by *Charles H. Burnett*). Chapel Hill, North Carolina. ***page 115***
4. **Adventure in Pedagogy**
   George E. Miller. Buffalo, New York. ***page 117***

Subsection on Renal Disease and Electrolyte Metabolism

West Room, Haddon Hall, 8 p.m., Sunday, April 29, 1956

Neal S. Bricker, *Chairman, Presiding*

1. **The Relationship of Bacterial Species to the Pathogenesis of Hematogenous Pyelonephritis**
   *A. I. Braude, A. P. Shapiro, and J. Siemienski.** The University of Texas Southwestern Medical School, Dallas. ***page 143***
2. **The Relationship between Plasma Osmolality and Concentration in Disease States**
   Albert L. Rubin, Warren S. Braveman,* Richard L. Dexter,* Parker Vanamee, and Kathleen E. Roberts* (introduced by *Thomas P. Almy*). Cornell University Medical College, Second (Cornell) Medical Division, Bellevue Hospital, Sloan-Kettering Institute, New York. ***page 129***
3. **Alterations in Renal Concentrating Ability Produced by Diet**
   Franklin H. Epstein and Charles R. Kleeman. Yale University School of Medicine, New Haven. ***page 137***
4. **The In Vivo Estimation of Renal Weight in Man: Physiologic and Pathologic Aspects**
   A. P. Crosley, Jr., J. F. Brown, D. A. Emanuel,* H. Tuchman, C. Castillo,* and G. G. Rowe.* University of Wisconsin Medical School, Madison. ***page 135***
5. **The Nature of Cation Accumulation by Muscle Cells: The Displacement of Potassium by Rubidium and Cesium**
   Arnold S. Relman, Anne T. Lambie, Arlene M. Roy* and Belton A. Burrows.* Boston. ***page 150***

Advance Research Reports Submitted to the Annual

National Meeting

of the

American Federation for Clinical Research

Steel Pier Theater, Atlantic City, New Jersey · Sunday, April 29, 1956

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BLOOD

A Rational Therapy of Systemic Lupus Erythematosus

By *N. B. Kurnick*. Department of Medicine, University of California at Los Angeles and the V. A. Hospital, Long Beach.

(Aided by grants from the American Cancer Society, Life Insurance Medical Research Fund, and California Division, American Cancer Society.)

Our studies on the mechanism of the LE cell phenomenon have led to the conclusion that the abnormal factor in the γ-globulin of the patient alters the cell membrane, admitting a serum proteolytic enzyme (in fraction III) into the cell, which destroys the protein inhibitor of desoxyribonuclease (DNase). As a consequence, the enzyme is liberated, attacks the chromosomal desoxyribonucleic acid, yielding the depolymerized nuclear mass which characterizes the phenomenon.

The inhibitor of DNase, in vitro, can penetrate the cell wall. Its addition to the LE serum-normal leukocyte system inhibits the LE cell phenomenon. Its intramuscular injection reduces circulating serum DNase activity for 48–72 hours.

We have treated a number of patients (16 with follow-up of 4 months or longer) with homologous fresh whole blood or leukocyte homogenates intramuscularly. The lysis of the infused leukocytes provides: (1) leukocyte cell walls which may adsorb the abnormal circulating γ-globulin and (2) DNase inhibitor which replaces the intracellular inhibitor destroyed in the mechanism of the LE cell phenomenon. One patient was treated with leukocyte fractions containing DNase inhibitor but no cell particulates, cell particulates alone, and a mixture.

The results are encouraging. Skin lesions cleared and serum DNase activity fell within 1 week in all, although other manifestations continued rapid progression in one patient. LE cells disappeared, usually within 3–4 weeks. Arthralgias, myalgias and fever subsided within 1–2 months. Renal damage showed improvement in several patients, but 1 uremic patient died in uremic coma despite treatment. Steroids were successfully withdrawn in almost all cases, with temporary withdrawal symptoms in some.

A Simple Method for Measurement of Erythropoiesis

By *Arthur J. Samuels, Lyle Reinhardt, Bohdan Jelinek and Dorli Furrer*. Hospital for Tumors and Allied Diseases and Medical Research Institute, City of Hope Medical Center, Duarte, California.

A simple clinically-applicable method for measuring erythropoietic activity in man has not been available heretofore. Such a method seemed feasible from Grob's observations that the reappearance of erythrocyte cholinesterase (RBC-ChE) in man, following its inactivation by diisopropylfluorophosphate (DFP), occurs at the rate of 0.8%/day. This replacement rate represents the rate of production and release of newly-formed

erythrocytes from the marrow. In the present study a potentiometric method was employed to measure the RBC-ChE replacement rate after its depression by the daily intramuscular administration of 1.0 mg. of DFP in peanut oil for 6 to 8 days.

In 6 normal volunteers the average rate of replacement of RBC-ChE activity was also 0.8%/day (118 days). In 4 hematologically normal tuberculous patients the average rate was 1.0%/day (95 days).

In the remaining 18 patients with various hematologic disorders, the following rates were obtained. Negligible RBC-ChE replacement rates were observed in 3 patients with aplastic anemia. Normal reappearance rates were observed in 3 patients with iron deficiency despite increasing anemia. RBC-ChE replacement was markedly accelerated during the reticulocyte response in these patients following iron therapy. Normal rates were also observed in patients with chronic lymphocytic leukemia and polycythemia vera. Accelerated RBC-ChE replacement rates were observed in the remaining 9 patients with acute blood loss, lymphosarcoma, Hodgkin's disease and acute leukemia. A replacement rate of 11.1%/day was observed in 1 patient during the bone marrow recovery phase following temporary hypoplasia resulting from an overdose of a myelotoxic drug (TEM). By the method described the erythropoietic activity was safely and simply evaluated in human subjects.

The Plasma Erythropoietic Stimulating Factor

By *James W. Linman, Frank H. Bethell and Helena K. Tascott.* A.E.C. Biological Effects of Irradiation Laboratory and the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor. (Aided by a grant from the Atomic Energy Commission.)

The maintenance of a steady state with respect to the blood corpuscles is dependent upon controlling factors which, for the most part, are poorly understood. Among the regulatory influences is a factor in the plasma of anemic animals which has the property of stimulating erythropoiesis when injected into normal animals. The factor is present in extracts of boiled and perchloric acid precipitated plasma, is apparently nonprotein, nonantigenic and not species specific. These properties make possible the use of larger animals or human subjects as donors, and a convenient test animal (the rat) as recipient, thus conserving material and providing for a number of animals in each experiment.

In normal animals erythropoietic stimulation results in the production of great numbers of small erythrocytes of normal hemoglobin concentration, so that there is little or no rise in hemoglobin and packed cell volume. The bone marrow of recipient animals is characterized by erythrocytic hyperplasia involving all stages of red cell development. Although the dynamics of the process have not been observed, the changes in the bone marrow and blood suggest that the erythropoietic stimulating factor acts by increasing the rate and number of cellular divisions.

The elaboration of the factor by anemic animals is not dependent upon the presence of a regenerative marrow. Activity has been demonstrated in extracts of plasma of rabbits made anemic by total body x-ray, as well as by repeated bleeding and by the injection of phenylhydrazine. Anemia is not essential for the production of the factor since extracts of plasma of patients with either polycythemia vera or secondary polycythemia have been shown to possess erythropoietic stimulating properties.

An Evaluation of Deficient Storage Iron as a Cause of Nutritional Iron Deficiency Anemia in Infancy

By *Jane F. Desforges and Jean P. Dawson.* Rh Laboratory and the Pediatric Service, Boston City Hospital, Boston.

Several factors have been suggested as contributing to nutritional iron deficiency anemia in infancy. This study was undertaken to evaluate further the role played by decreased iron stores due to prematurity or inadequate maternal supply.

In a group of infants with demonstrable iron deficiency anemia, the importance of storage and dietary factors in the etiology of this disease was compared. Age, race, sex, birth weight, growth rate, duration of gestation, dietary pattern and general health were tabulated. The population was predominantly male and Negro, with an age span of 7 to 30 months. Dietary habits were abnormal in at least ⅔ of the patients while approximately half were premature by weight.

Maternal iron supplies in these infants were evaluated by history and by routine blood studies, serum iron and iron-binding capacity. Several mothers were found to have mild hypochromic anemia, and a further number had occult iron deficiency manifested by low serum iron with a normal binding capacity. However, in none was this found to be the only cause for the infant's iron deficiency. Moreover, a significant number had received iron therapy during pregnancy.

Multiple causes for this disease were found in at least half of the cases. Only rarely was low storage iron at birth considered the only basis for the anemia. Abnormal diet, alone or superimposed on inadequate stores, was the most common finding in these infants.

The studies suggest that iron stores at birth may play a part in the development of nutritional iron deficiency anemia. However, it also demonstrates that a combination of causes is often found, and that adequate stores at birth as demonstrated by maturity, normal maternal supplies and iron therapy during the last trimester do not prevent the development of anemia in the presence of abnormal diet or rapid growth rate.

The Effect of a Single Intravenous Injection of Hydrocortisone on Erythrocyte Electrolyte Exchanges

By *Edward Kessler, Sol S. Nelson, Nathan Elder, Carmen L. Rosano and William P. Nelson, III.* Department of Medicine and Medical Research Laboratory, V. A. Hospital, Albany, New York.

The present study was undertaken to ascertain the effects of hydrocortisone on electrolyte exchanges in human erythrocytes. Normal subjects were injected intravenously with 100 mg. of hydrocortisone sodium succinate in 2 ml. of N-saline. Specimens of venous blood were withdrawn prior to and 30, 60, 120, 180 and 240 minutes after injection. Hematocrit, pH, sodium, potassium and water concentrations were determined on plasma and whole blood. Erythrocyte concentrations of sodium and potassium were calculated as mEq./L. of red cell water.

Nine of 10 subjects exhibited a significant rise in erythrocyte sodium concentration which was sustained for 30–60 minutes; no change developed in erythrocyte concentration of potassium or water. The concentration of sodium, potassium and water of plasma showed no consistent change; in 6 of the 7 subjects in whom pH of plasma was determined, a small but significant increase occurred which was sustained for 60–180 minutes. One experimental and 5 control subjects who were injected with 2 ml. of N-saline demonstrated no consistent alterations in any modality.

To characterize further the rapidity of these alterations, 8 subjects were studied at 5 to 10-minute intervals for 60 minutes. Erythrocyte sodium concentration rose, with the most marked increases occurring from 20–40 minutes postinjection; no change in erythrocyte potassium or water concentration occurred. Small but significant increases in plasma pH developed within 10–20 minutes; no change in sodium, potassium or water concentrations of plasma developed.

The results indicate that a single intravenous injection of hydrocortisone produces a transitory shift of sodium into erythrocytes, and a temporary rise in plasma pH, without any other consistent electrolyte shifts.

Alterations Produced by Polyvalent Cation at the Surface of Normal Human Erythrocytes

By *John F. Bertles and Frank W. Furth.* Department of Medicine, University of Rochester School of Medicine, Rochester, New York.

The influence of polyvalent cations on agglutination and precipitation has long been recognized. Various cations, in proper concentrations, promote agglutination of erythrocytes by high dilutions of specific antisera; higher concentrations of cation may produce agglutination in the absence of antiserum. The exact mechanisms of these actions are unknown. Jandl has shown that addition of chromic or ferric salts to suspensions of normal human erythrocytes in autogenous serum renders these cells agglutinable by antiglobulin serum.

Jandl's observation was confirmed. Neither the presence of heat-labile serum components nor the acidifying effect of chromic ion was directly responsible for the cells' altered capacity to react with antiglobulin serum. Raising the pH of the Cr-cell mixture reduced agglutinability by antiglobulin serum, presumably by lowering the effective cation concentration through further complexing with hydroxyl groups. Furthermore, when suspensions of normal human erythrocytes in unbuffered saline were "treated" with $CrCl_3$, washed, added to autogenous serum and rewashed, they too were strongly agglutinable by antiglobulin serum. Indeed, the cells were weakly agglutinable by antiglobulin serum even when the step of adding autogenous serum was omitted. Appropriate controls were employed. Gamma globulin or autogenous serum in high dilution completely neutralized the antiglobulin reaction. "Treatment" of normal erythrocytes in saline with $CrCl_3$ did not prevent subsequent sensitization by incomplete anti-D.

Tracing the chromic ion complex with $Cr^{51}Cl_3$ revealed that in the absence of serum the greater proportion of radioactivity located with the cells, nearly all in the stroma fraction.

The action of chromic "ions" may be analogous to the tanning of collagen by chromium. Chromic ion complex may interact with components, presumably protein, at the erythrocyte surface in such manner that, eventually, antibody specific for human globulin is attracted. Further studies directed particularly toward erythrocyte surface reactive groups are in progress.

Radioiron Determination of Human Erythrocyte Life-Span Distribution

By *Myron Pollycove, Paul J. Elmlinger, Louis A. Sarkes, Leonard Apt and Joseph F. Ross.* Radioisotope Unit, Boston V.A. Hospital, and Donner Laboratory and Donner Pavilion, University of California, Berkeley.

This study applies a new mathematic method of analyzing a transient decrease of erythrocyte radioiron to obtain accurately, not only the mean life span, but the entire erythrocyte life-span distribution. Since plasma radioiron is normally almost completely utilized for rapid in vivo labeling of erythrocytes, this method overcomes the basic defects of both the Ashby method and the slow, persistent erythrocyte labeling with slurred isotopic release inherent in the isotopic glycine method.

Following the intravenous injection of tracer radioiron into 4 normal subjects, erythrocyte radioactivity was measured for 5 months. Eighty % of

the labeling occurred within a 3–5-day period after injection. Erythrocyte radioiron remained constant at over 90% for approximately 100 days. A gradual decrease in erythrocyte radioiron then occurred until a minimum of 65–80% was reached 120–128 days following injection, then increasing to 84–91% within 9–23 days.

Analysis of erythrocyte radioiron revealed symmetric life-span distributions in 3 young subjects of 115 ± 17, 119 ± 12 and 122 ± 24 days. In 2 of these subjects no delay was measured between erythrocyte death and reappearance of radioiron in the plasma. In 1 subject a delay of 2 days was measured. A middle-aged subject had an asymmetric life-span distribution about the mean of 120 days.

Prolonged measurement of erythrocyte radioiron has also been applied to over 40 anemic patients with a wide variety of diseases. Significant shortening of the mean life span was readily detected and the degree of random destruction quantitated.

Following a single injection of radioiron, mathematic analysis of the transient erythrocyte radioiron decrease after in vivo labeling makes available an accurate and relatively simple means by which erythrocyte life-span distributions may be measured, in addition to quantitating hemoglobin formation and determining the sites of erythrocyte formation and destruction by in vivo counting.

The Measurement of Erythrocyte Survival with P^{32}-Tagged Diisopropylfluorophosphonate (DFP^{32})

By *Klaus Mayer and Allyn B. Ley.* New York City.

Methods currently in use for the study of the in vivo survival of autogenous red blood cells depend either on cumbersome technics involving isotopes with long half-lives or on simpler technics involving isotopic compounds which form imperfectly stable attachment to intact erythrocytes. The ideal tagging agent for such studies would be one which may be attached to the cell with a minimum of manipulation, which bears an isotope easy to count with a reasonably short half-life, and which persists in or on the red cell until lysis, and is not then reincorporated into other erythrocytes.

The presence in erythrocytes of cholinesterase, with which DFP forms an avid and irreversible bond, suggested to Cohen and Warringa the use of P^{32}-tagged DFP for studies of erythrocyte survival; and in studies on 2 normal individuals they reported a linear disappearance of P^{32}-tagged red cells with an end point at about 120 days.

With DFP^{32} prepared by the Dutch Medical Biological Laboratory, in vitro studies on the incorporation of the tag into normal red blood cells under various conditions were done. Uptake of the material varied between 10 and 28% and appeared to localize almost entirely in the stroma.

Three subjects were given approximately 100 μc. (i.m.) of DFP^{32} suspended in peanut oil. No significant toxic symptoms were observed. Serial measurements were performed on urine, plasma and erythrocyte radioactivity. After a rapid initial urinary excretion, a relatively constant excretion was observed of approximately 0.3% of the initial dose per day. The plasma was clear of activity in 3 to 4 weeks. Approximately 10% of the initial dose promptly appeared in the circulating erythrocytes, and the erythrocyte radioactivity disappeared in a linear fashion with an end point, by extrapolation, at about 120 days.

The Critical Role of Potassium in the Sickling Phenomenon

By *Robert C. Griggs and John W. Harris.* Department of Medicine, Cleveland City Hospital and Western Reserve University School of Medicine, Cleveland.

The present study demonstrates that the intracellular potassium ion concentration (K^+) is a critical factor in the sickling of erythrocytes from patients with sickle cell anemia; tactoid and gel formation in solutions of sickle hemoglobin were also found dependent upon a critical K^+.

It has been shown that sickle cells lose potassium at an abnormally increased rate when in the sickled form. In the present study cells were made K-deficient by maintaining them in the sickled form at a low oxygen tension and removing the accumulated K from the media. These cells readily returned to the discoid shape when oxygenated, but did not sickle when the oxygen tension was again reduced. When K was added to the media, the cells were again capable of sickling.

Solutions of sickle hemoglobin made from K-deficient cells, solutions made K-deficient by dialysis or from crystallized sickle hemoglobin where K had been excluded did not gel or form tactoids upon deoxygenation unless K was replaced. With gelling upon complete deoxygenation as the end point, a critical relationship existed between the concentration of sickle hemoglobin, pH, and K^+ in these solutions. With a sickle hemoglobin concentration greater than 30 Gm./100 ml. and a pH of 6.5, the solutions would gel with no measurable K. However, at a higher pH or with a lower sickle hemoglobin concentration, K was essential for gelling. At values of hemoglobin concentration and pH that occur within the intact cell, a K^+ of 80–100 mEq./L. is essential for tactoid and gel formation. Lithium ions would substitute for potassium; sodium, cesium, rubidium, calcium, magnesium and ammonium ions would not.

Previous studies have shown the importance of oxygen tension, hemoglobin concentration and pH in the sickling process; the critical role of potassium ion concentration is here demonstrated.

Apparent Renal Defect in Sicklemic Individuals

By *J. McMaster, C. J. Zarafonetis, L. Molthan and W. A. Steiger.* Department of Medicine, Temple University School of Medicine, Philadelphia.

Renal function studies were performed in 16 patients with sickle cell anemia, 33 with sickle cell trait, 2 with mixed sickle cell trait-thalassemia trait, and 1 with mixed sickle cell and hemoglobin C traits. Whenever possible other members of the subjects' families were studied. In this manner, nonsickling and genetic relationships could also be considered.

All patients had complete hematologic evaluation, including 4 tests for sickling. Determination of fetal hemoglobin, hemoglobin electrophoresis, and blood group genotyping was performed in many instances.

Complete urinalyses, 18-hour concentration tests, and maximum osmotic pressure of the urine as determined by freezing point depression were performed in all cases. Blood urea nitrogen and creatinine determinations, Addis counts, urea and endogenous creatinine clearance tests, and phenolsulfonphthalein excretion at 20, 40 and 60 minutes after intravenous dye (6 mg.) were done in the majority of subjects, while intravenous pyelography and Hickey-Hare tests were performed in selected cases.

Mean values for the clinical tests of renal function were well within limits of normal except for a limited ability to excrete a concentrated urine after fluid deprivation for 18 hours. This defect was more pronounced in sickle cell anemia than in sickle cell trait subjects; the mean maximum urine osmotic pressure was 421 mOsm./L. in the former, and 604 mOsm./L. in the latter.

Of the 52 individuals studied, whether sickle cell trait or sickle cell anemia, 48 exhibited a defect in urine concentration function. That this phenomenon may have a genetic basis is suggested by its uniformity of occurrence, and may be supported by family studies.

It is considered that the lesion is renal, of physiologic or metabolic nature, and inheritable as part of the sicklemic state.

The Rapid Destruction of Sequestered Red Cells as Determined with Fe^{59}-Labeled Human Reticulocytes

By *James H. Jandl.* Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical Scoool, Boston.

Red cells sensitized with incomplete antibodies were found previously to be sequestered specifically by the spleen with little or no associated hemoglobinemia. A means of determining the subsequent fate of such sequestered red cells was suggested by the known ability of reticulocyte-rich peripheral blood to incorporate Fe^{59} in vitro. During one hour's incubation of such red cells with autologous heparinized plasma previously incubated with $Fe^{59}Cl_3$, each cubic centimeter of reticulocytes became labeled with from 1 to 4 μc. of Fe^{59}, 60 to 80% of which was in the heme fraction and all of which remained within the reticulocytes despite 18 hours of subsequent incubation in plasma in vitro.

Hemoglobin derived from reticulocytes labeled with Fe^{59} was injected intravenously into normal subjects. Much of this Fe^{59} was deposited initially in the liver, as indicated by body surface radioactivity. Fe^{59} derived from labeled hemoglobin commenced to be reutilized by newly-formed red cells 24 hours after injection. Fe^{59}-labeled red cells either sensitized or agglutinated in vitro with various anti-D sera were rapidly sequestered by the spleens or by the livers, respectively, of normal subjects; in either instance, following a transient rise in the plasma Fe^{59} level and a diminution of organ radioactivity, red cell reutilization of Fe^{59} began between 34 and 36 hours after injection into normal subjects, and within 8 hours after injection into a patient with acquired hemolytic anemia. Since radioactivity had not reappeared in circulating red cells after the injection of sensitized Cr^{51}-labeled red cells, and since the Fe^{59} tag remained in red cells despite prolonged incubation in vitro, the release within hours of Fe^{59} from the sequestering organ in vivo indicates a rapidly-acting lytic mechanism within these intact tissues, operative against sequestered red cells.

A Splenic Hemolytic System of Lipidic Nature in Man

By *Sergio I. Magalini, William Blumenthal and Mario Stefanini.* Joseph Stanton Memorial Laboratories, Saint Elizabeth's Hospital and Department of Medicine, Tufts University School of Medicine, Boston.

Successive extractions with benzene and acetone of homogenized blood-free pulp from 4 normal surgical spleens yielded a fraction exhibiting strong hemolytic activity when incubated with washed normal erythrocytes. Benzene fraction was further studied by chromatopile (acetone as mobile phase). Fast migrating phase contained all hemolytic activity. This was again fractionated in chromatopile (70% methanol in water as mobile phase), highest hemolytic activity being detected in fraction migrating with longer chain fatty acids and neutral fats. Small amount of hemolytic agent was eluted from other areas, not containing neutral fat. Thus, hemolytic activity appeared related predominantly to fatty acids, perhaps of longer chain. Destruction of

erythrocytes incubated with purified hemolytic agent was preceded by marked increase of spherocytes. Preliminary studies showed platelets to be destroyed by hemolytic fraction also. Under our conditions, other tissues failed to yield a hemolytic agent.

Residue of spleen after benzene and acetone extraction was treated with 4:1 chloroform-methanol mixture and yielded a fraction inhibiting activity of the hemolytic agent, insoluble in acetone and benzene; thus, presumably, a phospholipid. Serum also inhibited activity of the hemolytic agent; this action was related mostly to protein constituents; slight inhibition was obtained from acetone insoluble lipid fraction.

Studies, thus far, have been completed on 10 surgical spleens from patients with various hematologic disorders. Hemolytic activity far exceeding normal was recovered from the spleen of 2 patients. One was suffering from acquired hemolytic anemia and hyperlipemia; the other from idiopathic thrombocytopenic purpura. In the latter, however, anemia in absence of bleeding, reticulocytosis and bone marrow erythroid hyperplasia indicated increased hemolysis.

Thus, the balanced hemolytic system we describe may operate in physiologic breakdown of effete red blood cells; in pathologic conditions, its imbalance may represent a third mechanism of destruction of erythrocytes and, perhaps, of other formed blood elements in addition to autoimmune processes—phagocytosis.

Treatment of Acquired Hemolytic Anemia with prednisone (Meticorten)

By *Russell Weisman, Jr., John W. Harris, Wayne H. Borges and Robert C. Griggs.* Departments of Medicine and Pediatrics, Western Reserve University and University Hospital and Cleveland City Hospital, Cleveland.

A decrease in hemolysis was observed in 5 of 6 patients with acquired hemolytic anemia during treatment with prednisone. Two patients had chronic lymphatic leukemia; the other 4 had idiopathic hemolytic anemia for which splenectomies had been performed previously in 2. One child in the group and 1 patient with leukemia were splenectomized during the course of this study.

One patient with leukemia was controlled well with 45 mg. of prednisone daily. The second patient with leukemia, who could not be maintained on cortisone because of toxic symptoms, did respond moderately well to prednisone (45 mg. daily). He relapsed on therapy, was then splenectomized, and had a remission in the hemolytic process. No antileukemic effect was observed in either patient during prednisone therapy.

All 4 patients with idiopathic hemolytic anemia responded favorably to prednisone in daily doses of 40 to 75 mg. Two continued to have increased osmotic and mechanical fragility of erythrocytes and high antiglobulin titers, but each had a lengthened erythrocyte autosurvival time during treatment as demonstrated by the Cr^{51} technic. Three of these patients remain in remission 4 to 8 weeks after withdrawal of prednisone.

A girl of 8, who has been maintained on steroid therapy for 11 months, is the only patient showing significant toxic effects from prednisone. Her hemolytic process improved initially when she received 300 mg. of cortisone daily. She relapsed on this regime, was splenectomized without benefit, but finally responded, and maintained a normal hemoglobin level, while receiving 75 mg. of prednisone daily. She now has a Cushing-like appearance, has gained 20 Kg., and has compression fractures of 2 thoracic vertebrae. Although several previous attempts to reduce the maintenance dose were associated with rapid declines in hemoglobin, a satisfactory level is now being maintained with 25 mg. of prednisone daily.

The Relation of Neoplastic Tissue Antigens to "Autoimmune" Hematologic Syndromes

By *Mario Stefanini, Sergio I. Magalini and James H. Patterson.* Joseph Stanton Memorial Laboratories, Saint Elizabeth's Hospital and Department of Medicine, Tufts University, School of Medicine, Boston.

Anemia, leukopenia and thrombocytopenia may occur in patients with disseminated malignancies. They may follow bone marrow replacement with foreign tissue; in other instances, however, bone marrow appears hyperplastic and unaffected by tumor. Auto and isoantibodies against erythrocytes, leukocytes or platelets were detected in good percentage in such cases presenting hemolytic anemia, leukopenia or thrombocytopenia, respectively. In several instances, thrombocytopenia and, in one case, leukopenia were transitorily reproduced in normal individuals receiving 250 ml. or more (i.v.) of patient's plasma.

Detailed studies were conducted to investigate the mechanism of development of erythrocyte and platelet antibodies in the following cases: (a) 2 patients with metastatic prostatic carcinoma and 1 patient with metastatic breast carcinoma, previously splenectomized unsuccessfully. All presented severe thrombocytopenia with normal complement of megakaryocytes in the bone marrow and high titer platelet agglutinin in their serum; (b) 1 patient with reticulum cell sarcoma and acquired autoimmune hemolytic anemia, also splenectomized unsuccessfully. Tumor tissue became available through surgery. Fresh autopsy tissue served as control. Patients' sera were absorbed with the individual's own malignant tissue, malignant tissue of identical

histologic type from other donors and normal tissue from individuals with identical blood group.

Platelet agglutinin titer: (a) decreased consistently and markedly after absorption of serum with patient's own neoplastic tissue and, in some instances, with homologous neoplastic tissue; (b) decreased in inconstant and insignificant fashion after absorption with normal tissue. The auto- and isoerythrocyte antibodies in the patient with reticulum cell sarcoma were absorbed by tissue from tumoral nodules, not by the surrounding splenic tissue. In this patient, hemolytic anemia continued after splenectomy. Later, autopsy showed extensive involvement of all organs.

These studies suggest that neoplastic tissue may represent an antigenic stimulus to the formation of antibodies against formed blood elements; perhaps, antigens common to cancer and blood cells are responsible for the development of such antibodies.

Hereditary Spherocytosis in the Mouse: An Experimental Model

By *A. G. Motulsky, R. Anderson and R. Huestis.* Department of Medicine, University of Washington, and the Department of Biology, University of Oregon, Eugene.

A genetic disease closely resembling human hereditary spherocytosis exists in the deer mouse. The syndrome is a compensated hemolytic disease characterized by neonatal jaundice, spherocytosis, increased osmotic fragility, reticulocytosis, bone marrow hyperplasia and splenomegaly. Inheritance is recessive. Three categories of animals are thus available for study: affected homozygotes, heretozygotes and normal field mice.

Erythrocytes from normal donors were transfused to normal mice and their destruction measured by the Cr^{51} technic. The mean half-time of Cr^{51} was 8.8 days ± 15% (σ) in 8 observations. Red cells from heterozygotic animals could not be distinguished from normals by this technic (mean half-time of Cr^{51}: 8.6 days ± 22% in 5 observations).

Red cell survival from affected homozygotic donors was significantly shortened when transfused to splenomegalic homozygotes (mean half-time of Cr^{51}: 4.1 days ± 28% in 12 observations) as well as in recipients with normal spleens (mean half-time of Cr^{51}: 3.0 days ± 23% in 7 observations). The reverse experiment of transfusing cells from heterozygotic and normal animals into splenomegalic homozygotes gave normal results (mean half-time of Cr^{51}: 8.8 days ± 27% in 6 observations).

Splenectomy in affected animals resulted in markedly decreased hemolytic rates. Thus, when homozygous cells were transfused into splenectomized mice, survival times became normal (mean half-time of Cr^{51}: 8.3 days ± 16% in 11 observations). In a few splenectomized recipients where survival time determinations did not return to normal, small but significant amounts of splenic tissue were found at postmortem examination.

In these mice splenomegaly is a secondary phenomenon. Any spleen, whether large, normal or small will trap and destroy hereditary spherocytes. Normal cells survive normally in affected recipients in spite of splenomegaly. Splenectomy removes the splenic trap and allows normal or almost normal survival of the genetically abnormal cells. These findings clarify splenic-erythrocytic interaction in hereditary spherocytosis, since the mouse syndrome appears to parallel the human disease.

The Incidence of Blood Group A in Pernicious Anemia

By *William P. Creger and A. T. Sortor.* Department of Medicine, Stanford University School of Medicine, San Francisco.

A survey of three university hospitals in San Francisco yielded 115 patients who met strict criteria for diagnosis of pernicious anemia and had recorded blood group determination. Of these patients, 51.3% were found to be of blood group A, while of 20,070 normal blood donors from the same area, 38.1% were found to be of blood group A.

This 35% increase in percentage of blood group A in pernicious anemia over that in normal subjects is 3 times the increase in percentage in blood group A that has been reported in persons with cancer of the stomach.

The view is advanced that the heightened occurrence of blood group A in pernicious anemia is not identical in significance with the hair and eye color, and ethnic origin of persons with this disorder. It is also suggested that both gastric cancer and pernicious anemia may be related to the occurrence of blood group A rather than being directly related to each other.

Certain hypotheses are offered as to possible pathophysiologic relationships of the blood group finding to the pathogenesis of both pernicious anemia and cancer of the stomach.

Vitamin B_{12} Absorption: Clinical Evaluation of the Schilling Test

By *Alfred Doscherholmen and Paul S. Hagen.* Department of Medicine, University of Minnesota Medical School and the Hematology Section, Medical Service, V. A. Hospital, Minneapolis.

Because a false positive urinary excretion test has been encountered, a clinical appraisal of the value of this test has been undertaken by comparing the results with those obtained by the fecal excretion method (Heinle) performed simultaneously on the same patients. Three different test doses of labeled vitamin B_{12} were used: 0.1, 0.5 and 1.0 μg. containing from 0.02 μc. to 0.07 μc. of Co^{60}. The first dose appeared to give the most satisfactory results with

both the Schilling and the Heinle methods. As the tracer dose increased, the average stool excretion figure increased and the average urine excretion figure decreased. The average stool excretion figure in 68 tests on 56 nonpernicious anemia subjects was 37.6%, and urine excretion 23.7%. In 29 tests performed on 21 patients with pernicious anemia the average stool excretion was 78.5% and the urine excretion 0.3%. Three patients with intestinal megaloblastic anemias excreted from 80.5 to 93.9% in the stool and nothing in the urine. While the excretion pattern was converted to normal in patients with pernicious anemia and total gastrectomy with the addition of a potent intrinsic factor concentrate, there was no change in the stool and urinary findings in the patients with intestinal disorders. Several factors have been found to influence the result of both the Heinle and the Schilling test, and false-negative as well as false-positive tests can be encountered with both methods. In this series the Heinle test gave overlapping in 9 out of 97 tests, while no overlapping was found in the Schilling test. A false-positive Schilling test was encountered in 1 instance.

Although the Schilling test on rare occasions may be falsely positive, it appears to be a reliable test in the diagnosis of pernicious anemia.

Megakaryocyte Glycogen in 14 Young Adults

By *Harry W. Daniell.* Department of Pharmacology, University of Vermont, Burlington

A close correlation has been demonstrated between the state of erythropoiesis and the megakaryocyte glycogen content of the bone marrow. This has been possible through the development of a semiquantitative method for determining the megakaryocyte glycogen content in aspirated marrow, which consists of scoring (from 0 to 4) the glycogen demonstrated by the periodic acid Schiff technic in each of at least 50 megakaryocytes, and adding the scores of these cells. Results are expressed in terms of 100 cells, as the MGS (megakaryocyte glycogen score). This determination has been completed on 200 persons in whom detailed clinical histories and laboratory data are known. Included in this group are 14 healthy young adult volunteers. Correlation between the MGS and the state of erythropoiesis has been demonstrated in both the "normals" and in the patients representing a wide range of hematologic disorders. This correlation is closer than that between erythropoiesis and either the reticulocyte count or the bone marrow differential count.

Those volunteers with recent menses, recent 500 cc. venesection or repeated blood donations over a period of several years had higher megakaryocyte glycogen scores than those without such a history. The hematocrit, RBC, WBC, leukocyte differential, platelet and reticulocyte counts of the peripheral blood, and differential counts of marrow aspirate were normal in all cases.

Preliminary observations indicate elevations of the MGS in active polycythemia vera, iron-deficiency anemia, hemolytic anemias, acute or chronic blood loss, active pulmonary tuberculosis and some atypical collagen diseases. Decreases in the MGS appear to be consistently present in "burned out" polycythemia, aplastic and hypoplastic anemias, untreated pernicious anemia, some acute viral infections, hypersplenism, disseminated lupus erythematosus and thrombotic thrombocytopenic purpura.

Changes in Platelet Morphology during Coagulation

By *Soonu S. Setna and Robert L. Rosenthal.* Laboratories of the Levy Foundation, Beth Israel Hospital, New York City. (Aided by grants from the National Heart Institute and the Dazian Foundation.)

Morphologic alterations of platelets during blood coagulation were studied by the phase contrast microscope. A drop of 0.025 M calcium chloride was added to a drop of normal platelet rich citrated plasma and a cover slip was placed on the preparation. When the preparation was studied under the phase contrast microscope, the first observed change was an alteration in platelet form from normal (round, oval, oblong, dumb-bell, bean, crescent, triangular, drop, leaf, quadrangular, irregular) to a small round form. The chromomere, which was at first in the center of the platelet, moved toward the periphery, became eccentric in position, and the platelet assumed a "signet ring" appearance. The chromomere became granular and the individual granules exhibited motion. Neighboring platelets then clumped together at the point of their eccentric chromomeres to form a "rosette" pattern. The "petals" or periphery of the rosettes were formed by the veils of the agglutinated platelets. Fibrin strands then began to appear in-between and around the platelets, and attached themselves to the center of the rosette or the clumped chromomeres.

As coagulation proceeded, the veils separated from the clumped chromomeres and lay at the periphery of the rosette, around the chromomere material from which they were shed. The fibrin strands remained attached to the clumped chromomeres. After some hours, a dense fibrin network formed, The platelet material (chromomere), which was attached to the fibrin strands, had shrunk, while the shed veils lay in the interstices of the network and could be seen only with difficulty.

In the absence of a normal network, as in a case of hypofibrinogenemia, the loose round veils floated around freely in the plasma. The clumped chromomeres, with their adherent fibrin and a few veils caught in this scanty mesh, remained attached to the glass surface.

Thromboplastin-Thrombin Generation Test: Technic and Application

By *O. Herman Dreskin*. Departments of Internal Medicine and Pathology, Jewish Hospital, Cincinnati, Ohio.

The thromboplastin generation test of MacFarlane and Biggs has become a valuable tool in the study of coagulation defects. It has permitted localization of the deficiency to plasma, serum or platelet fractions of blood. It has admirably supplemented the prothrombin consumption test. However, the technic is tedious and difficult. Suspensions of washed platelets are quite variable, and their concentrations are unphysiologically high in this test. The serum fraction contains small but definite amounts of prothrombin, and, consequently, thrombin as well as thromboplastin is generated, and the potency of this natural thromboplastin is moderately or tremendously enhanced by the varying original amount of serum prothrombin.

The present technic preserves the essential features of thromboplastin generation but adds a large and reproducible amount of thrombin generation. Whole blood, calcium chloride solution, and a fibrinogen solution are the only reagents required for the test. Platelets are supplied in fairly constant, untraumatized, and physiologic concentration by the whole oxalated or citrated blood.

Reagents: (1) 4.5 ml. blood in 0.5 ml., 0.1 M, sodium oxalate or 4% sodium citrate (siliconized syringes and test tubes preferable).

(2) Calcium chloride (anhydrous), 0.02 M, in 0.53% saline solution.

(3) Pooled oxalated plasmas, fresh, 5.0 ml. Add 1.0 ml. 30% barium sulfate suspension. Incubate 10 minutes at 37°C. (This prothrombin-free plasma is the fibrinogen solution.)

Technique: To 0.2 ml. oxalated blood at 37°C. add 4.8 ml., 0.02 M, calcium chloride in 0.53% saline. At intervals of 6, 10, 14 and 18 minutes take 0.2 ml. aliquots and add to 0.2 ml. barium plasma at 37°C. and determine clotting time. The shortest clotting time represents maximum thromboplastin and thrombin generation, and is usually 10 minutes for normal bloods.

When thromboplastin-thrombin generation is impaired, as represented by an 18 minute or longer end point, specific entities are mapped out by repeating the test with addition of normal saline-washed blood (representing platelets), normal barium plasma or normal serum.

Development of an Anticoagulant in Congenital SPCA Deficiency

By *Edmund W. Campbell, Asuman B. Unugur and Hugh H. Fudenberg*. Blood Research Laboratory, New England Center Hospital and Department of Medicine, Tufts Medical School, Boston.

A 33-year-old male with a definite congenital hemorrhagic disorder was evaluated. This patient has been studied several times and the diagnosis of congenital SPCA (proconvertin) deficiency was established. One paternal uncle had died from hemorrhage following surgery.

The patient was evaluated and prepared for cholecystectomy because of severe gallbladder disease leading to drug addiction. Repeated hemorrhagic surveys revealed moderate prolongation of the silicone clotting time, clotting time of recalcified plasma and increased plasma prothrombin times. SPCA activity was 15 to 20%. A decrease in prothrombin utilization, accompanied by an abnormal thromboplastin generation curve in serum was present. Platelet counts, platelet agglutinin study, factors V and VI, clot retraction, bleeding time and fibrinogen were all normal. Matching experiments against normal stored serum and plasma and similar experiments using sera and plasma from patients with known hemophilia, PTC and PTA deficiency revealed complete mutual correction. No correction was obtained utilizing normal serum and plasma treated with barium sulfate or untreated serum and plasma from a dicumarolized patient. In vivo correction was obtained by transfusion of normal stored plasma and serum.

Upon complete correction, an uneventful cholecystectomy was performed. However, profuse bleeding ensued 1 hour after surgery, which was controlled by transfusions. Multiple complications arose, including the development of several minor group erythrocyte antibodies, 1 of which remains to be fully classified.

A striking decrease in the corrective effect of transfusion (serum or plasma) and an anticoagulant was definitely demonstrated by in vitro study. This anticoagulant appeared specific, similar to that phenomenon occurring in hemophilia following multiple transfusions.

This study has been presented to emphasize the serious complications occurring following surgery in this congenital coagulation defect even though meticulous preparation was emphasized. Of interest was the rapid utilization of SPCA when the demand was brought on by surgery. However, of particular interest is the inducement of an anticoagulant acting against SPCA when this substance is supplied artificially in congenital SPCA deficiency.

Low Fibrinogen without Fibrinolysis in Prostatic Carcinoma

By *N. Raphael Shulman*. Naval Medical Research Institute, Bethesda, Maryland

Observations were made on a patient with prostatic carcinoma who developed hypofibrinogenemia, hypoprothrombinemia and thrombocytopenia without fibrinolysis. Since there was no active

bleeding, an unusual opportunity was presented for experimentation.

This case of hypofibrinogenemia was similar to those showing concomitant fibrinolysis in which the enzyme is considered to digest coagulation factors. Since there was no fibrinolysis in this instance, and since we have demonstrated in other cases of fibrinolysis that the enzyme digests only fibrin but not fibrinogen or other clotting factors, it appears that the simultaneous occurrence of fibrinolysis and a coagulation defect may be fortuitous, and that proteolytic activity does not cause the coagulation defect.

Two transfusions of 4 Gm. of fibrinogen were given during a period when the patient's fibrinogen was stabilized at 20–30 mg. %. The half-life was very short (1 and 2½ days, respectively). Assuming that fibrinogen was utilized at the measured rate, its production would have to be equally rapid in order to maintain any circulating fibrinogen. Intravascular coagulation seemed a possible explanation for the hypofibrinogenemia. Heparin was administered in amounts sufficient to maintain an infinite clotting time over a 13-hour period, with the expectation that the fibrinogen level would rise. However, fibrinogen and other clotting factors remained at the same low level. The failure of fibrinogen to increase during heparinization indicated either that fibrinogen removal continued by some process other than coagulation in the usual sense, or that fibrinogen synthesis was depressed. The short fibrinogen half-life could have represented increased utilization or rapid equilibration with depleted extravascular stores. Since liver function tests were normal, postulating depressed fibrinogen synthesis would not be in accord with current concepts of fibrinogen formation. On the other hand, postulating increased utilization would imply removal of fibrinogen by a mechanism unaffected by anticoagulants. We are attempting to clarify fibrinogen metabolism by in vivo administration of radioactively-tagged fibrinogen.

Observations on the Anemia of the Myelofibrosis-Myeloid Metaplasia Syndrome

By *Hugh Fudenberg, John P. Mahoney and William Dameshek.* Blood Research Laboratory, New England Center Hospital and Department of Medicine, Tufts Medical School, Boston.

Elevated reticulocyte, plasma hemoglobin, serum iron and bilirubin values in 12 patients with the myelofibrosis-myeloid metaplasia syndrome (M-MMS) suggested that a hemolytic mechanism was responsible, at least in part, for the anemia associated with this syndrome. The presence both of marked splenomegaly and of marked morphologic alterations in the erythrocytes with associated abnormalities in osmotic fragility warranted investigation of the relative roles of extracorpuscular and of intracorpuscular erythrocyte defects in the etiology of the accelerated erythrocyte destruction.

Accordingly, survival of normal red cells in 8 patients with myeloid metaplasia and of red cells from M-MMS patients in 8 normal recipients was studied after cross-transfusion of Cr^{51}-labeled red cells. The red cells of 4 of the M-MMS patients were also infused into 4 subjects splenectomized several years earlier because of trauma or ITP.

Red cell and plasma volumes and in vivo uptake of radioactivity by the spleen were also measured in 5 patients to evaluate the role of hemodilution and/or splenic sequestration of erythrocytes in the production of the low venous hematocrits observed.

Survival time of normal erythrocytes was, in general, considerably reduced in the myeloid metaplasia patients. Survival of myeloid metaplasia erythrocytes was likewise reduced after infusion into normal recipients; the survival of these erythrocytes was shortened to a lesser extent when infused into normal splenectomized individuals. In general, the intracorpuscular defect appeared to be more severe.

Red cell volume determinations revealed that the total body red cell mass was not as greatly reduced as would be expected from the reduction in the peripheral blood values, presumably because of pooling of high hematocrit blood in the large splenic reservoir, thus leading to alteration of the body hematocrit/venous hematocrit ratio. Further evidence for red cell sequestration was produced by results of measurements of in vivo radioactivity uptake over the spleen and other body organs.

These results indicate that the anemia of myeloid metaplasia is often, in part, caused by accelerated erythrocyte destruction resulting from both intracorpuscular erythrocyte defects and extracorpuscular hemolytic mechanisms. The reduction of the peripheral venous hematocrit is, in part, caused by pooling of erythrocytes in the large spleen.

The Viability of Transfused Leukocytes in Irradiated Rats

By *J. W. Hollingsworth, Stuart C. Finch and Paul B. Beeson.* Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut. (Aided by a grant from the U. S. P. H. S.)

By means of a cross-circulation technic, the viability of transfused normal and leukemic leukocytes was studied in rats. The results of these experiments indicate that functional transfused leukocytes may persist for long periods of time in certain intravascular sites, in spite of their rapid clearance rate from the arterial blood. These studies also suggest that the disappearance curve of transfused white cells from the circulation represents a redistribution rate rather than a destruction rate.

The technic employed was that of femoral artery and vein cross-circulation through nonwetting surfaces, so that blood flow could be controlled accurately. Normal and leukemic rats were crossed with normal and irradiation-induced leukopenic rats.

Morphologic evidence for rapid small vessel sequestration of the tranfused leukocytes was obtained through simultaneous study of arterial and tail blood samples. During cross-circulation, tail blood from the irradiated animals contained more leukocytes than did the arterial blood, and afterwards the tail counts invariably were higher than those of the irradiated controls. Leukemic cells were detected in the tail blood samples of the irradiated rats for periods up to 3 days after cross-circulation with leukemic donors. A few irradiated and normal recipient rats eventually developed leukemia. Additional studies indicated that the transfused white cells rather than some other blood factor were responsible for the difference in bacterial removal.

The Relation of Leukoagglutinins in Human Sera to Leukopenia and Blood Transfusions

By *Rose Payne*. Department of Medicine, Stanford University School of Medicine, San Francisco

It has been suggested that leukoagglutinins (L-As) may be related to the existence of an immunoleukopenia, but the failure to demonstrate autoactivity of the majority of L-As casts doubt on this relationship. The occurrence of L-As in patients who had a history of many transfusions suggested that they might be isoagglutinins. The present study was undertaken to clarify the relation of L-As to leukopenia and blood transfusions. The technic for demonstration was a modification of Dausset's method. The patients studied were: (1) those primarily leukopenic or neutropenic; (2) those with disorders in the categories already reported to have L-As, but who were not necessarily leukopenic or neutropenic; (3) random patients from hematology clinics; and (4) patients with a history of repeated transfusions.

L-As were demonstrated in the sera of 38 of 350 patients; they were not found in 50 students without history of transfusion. L-As were found in diseases not previously reported, as anemia of liver disease, myelofibrosis, neuroblastoma, and the blood loss anemia of esophageal varices and hiatus hernia. Neither leukopenia nor neutropenia occurred in a large number of patients in this series, which is at variance with a published report that 85% of patients with L-As were either leukopenic or neutropenic. At the time of testing, 65% of our patients with L-As had neither leukopenia nor neutropenia.

Prior to testing, 90% of the patients with L-As had had from 2 to 150 transfusions. The incidence of L-As increased directly with the number of transfusions. The L-As failed to react with autologous leukocytes; they reacted with most homologous leukocytes.

These data suggest, first, that the majority of L-As found by present methods are isoleukoagglutinins which may be the result of transfusions in individuals who are vigorous antibody manufacturers for leukocyte antigens; and, second, that L-As may occur frequently without leukopenia.

Antileukocytic Antibodies in Guinea Pigs Sensitized to Connective Tissue

By *V. Yakulis, P. Heller and H. J. Zimmerman*
V.A. Hospital, Chicago

Previous studies have led to the consideration that the LE plasma factor might be an antileukocytic antibody. In keeping with this has been the demonstration of nucleophagocytosis with or without the LE cell phenomenon in patients with drug hypersensitivity. In an attempt to correlate the primary histologic feature of systemic lupus erythematosus (namely, collagen degeneration) with the LE cell phenomenon, the present study was undertaken.

Guinea pigs were sensitized to antigens prepared from rabbit liver, leukocytes and connective tissue respectively. Their sera were studied at the end of 7 and 14 days for the presence of complement-fixing antibodies against rabbit liver, leukocytes and connective tissue and human liver, leukocytes and connective tissue. In all instances except the animals sensitized to connective tissues, the antibodies resulting from sensitization were specific for the homologous antigen, with only slight cross reactions. In the sera of the animals sensitized with connective tissue, extremely high titers of antibodies against human and rabbit leukocytes were found.

Behavior of Leukocyte Alkaline Phosphatase in Chronic Myelogenous Leukemia and Myeloid Metaplasia

By *J. J. Kenny, E. Wiltshaw and W. C. Moloney*. Hematology Laboratory, (Tufts First and Third Medical Services) Boston City Hospital, Boston. (Aided by a grant from the American Cancer Society.)

Investigation of leukocytic alkaline phosphatase by histochemical and biochemical methods reveals that following incubation in substrate for 1 hour approximately 25% of normal polymorphonuclear leukocytes demonstrate slight to moderate alkaline phosphatase activity, while in chronic myelogenous leukemia about 2% of morphologically similar cells became slightly positive. However, after 24 hours incubation, 80% of normal but only 20% of CML segmented neutrophils show evidence of cytoplasmic alkaline phosphatase activity.

In normal individuals with pyogenic infection almost all segmented neutrophils show strong

alkaline phosphatase activity. In contrast, patients with CML and pyogenic infection develop a moderately elevated alkaline phosphatase, but histochemical technics demonstrate this enzyme in only a small per cent of polymorphonuclear leukocytes. These observations suggest that in CML there are probably 2 populations of neutrophils: a group capable of normal alkaline phosphatase activity, indicated by the response to prolonged incubation and pyogenic infection, and a much larger population which is incapable of this cytoplasmic enzyme activity.

The effect of Myleran, x-ray, and P^{32} on leukocyte alkaline phosphatase has also been studied. In CML, during remission induced by Myleran, no rise in polymorphonuclear leukocyte alkaline phosphatase was observed. This suggests that the drug inhibited proliferation of both normal and abnormal myeloid precursors, and that, in remission, the same relative proportion of alkaline phosphatase negative and positive cells was maintained.

After P^{32}, Myleran, and x-ray therapy, a marked drop in total white blood cells occurred in cases of myeloid metaplasia. However, it was noted that the strongly positive alkaline phosphatase activity of practically all segmented neutrophils remained unchanged. Since therapy did not restore the normal distribution of alkaline phosphatase-containing leukocytes, it would seem that in this disorder a single cell population exists, and was uniformly affected by therapy.

Effect of p-(Di-2-Chloroethylamino)-Phenylbutyric Acid (Archlorethamine, CB 1348) in the Treatment of Chronic Lymphatic Leukemia and Certain Lymphomas

By *John E. Ultmann, George A. Hyman and Alfred Gelhorn.* Institute of Cancer Research, College of Physicians and Surgeons, Columbia University and the Medical Service of the Presbyterian Hospital and the Francis Delafield Hospital, New York City. (Aided by a grant from the U.S.P.H.S.)

Thirty patients were treated with p-(di-2-chloroethylamino)-phenylbutyric acid (Archlorethamine, CB 1348). Archlorethamine was administered orally in daily dosage ranges of 0.1 to 0.3 mg./Kg. body weight. An average course in most cases consisted of 6 mg./Kg.; the total effective dose, however, ranged from 50 to 900 mg.

Eighteen patients with symptomatic chronic lymphatic leukemia were given 20 courses of therapy. A significant fall in white blood cell count to less than 30% of initial values was observed in 14 instances. Of these, the percentage of lymphocytes was decreased by 25% or more in 5 patients, while a marked decrease in hepatosplenomegaly and lymph-node enlargement occurred in 7. Eight patients reported subjective improvement and return to normal activities. The results in 12 patients with various lymphomas (giant follicular lymphosarcoma, 1; lymphocytic lymphosarcoma, 5; and Hodgkin's disease, 6) were not encouraging, except in 3 patients (2 with lymphocytic lymphosarcoma, 1 with Hodgkin's disease) in whom partial improvement occurred.

The drug did not produce gastrointestinal side effects, nor hepatic or renal complications. Severe leukopenia and thrombocytopenia occurred in 1 instance. Of the 10 patients who died, 5 have come to autopsy. In all cases, there was evidence of widespread active disease. No evidence of drug toxicity was demonstrated in the liver or kidneys. Marrow hypoplasia occurred in 3 instances, but in 2 cases there was diffuse replacement by tumor tissue.

At present, Archlorethamine appears to be particularly useful in the treatment of patients with chronic lymphatic leukemia who have an initial platelet count below 100,000 which makes treatment with triethylenemelamine or nitrogen mustard hazardous. Further clinical study is needed to assay the ultimate value of this new nitrogen mustard.

A Sex Difference in the Response to Titrated Irradiation Therapy (P^{32}) of Patients with Chronic Granulocytic Leukemia

By *William H. Crosby and Robert D. Lange.* Department of Hematology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

In 14 consecutive patients with chronic granulocytic leukemia under treatment for 6 months or more with Osgood's program of "titrated, regularly spaced, total-body irradiation," the women required less P^{32} to control the disease. The average dose for all 7 women was 20 μc. of P^{32}/Kg. body weight/month; the average for the 7 men was 83 μc. There was no overlap between the 2 groups. The woman given the largest dose received 35 μc./Kg./month; the man who got the smallest dose received 50 μc. With the assumption that the only significant difference between the groups is sex, the difference of requirement for P^{32} is considered to be statistically significant. There is 1 possibility in 20 that this difference was due to chance selection of the patients, over which we had no control. While the reason for the difference is not known, it suggests that chronic granulocytic leukemia may be a less severe disease in women than it is in men.

Concurrent 6-Mercaptopurine and Cortisone Therapy in Acute Myelogenous Leukemia

By *Spenser S. Brewer, Evelyn V. Coonrad and R. Wayne Rundles.* Department of Medicine, Duke University School of Medicine, Durham.

The long-term results of a combined 6-mercaptopurine-cortisone regime have been studied in 23 patients with acute myelogenous leukemia.

Seven of the patients were 0–14 years of age, 7 from 15–30 years, and 9 from 31–73 years. In patients with leukopenia and/or thrombocytopenia, cortisone was given initially for a short period before starting the 6-mercaptopurine. In those with leukocytosis, splenomegaly and/or bone tenderness, the agents were started in the opposite order.

Our observations, somewhat at variance with current opinion, support the following conclusions: (1) A significant degree of clinical and hematologic improvement was produced in about 60% of patients regardless of their age. (2) Cortisone usually led to improved bone marrow function in patients with cytopenia(s). Adverse hematologic effects produced by steroid therapy were not observed. (3) The effect of 6-mercaptopurine and cortisone given concurrently was superior to that of either agent given alone, or used serially. (4) None of the patients who had become "resistant" to the cortisone-6-mercaptopurine regime were significantly benefited by the subsequent use of antifolic acid compounds or other agents.

Glycoproteins in Hematologic Disorders

By *Margarida N. de Magalhes, Sergio I. Magalini, Elly Moschides and Mario Stefanini.* Joseph Stanton Memorial Laboratories, Saint Elizabeth's Hospital, and the Department of Medicine, Tufts University School of Medicine, Boston.

Chemical determination of total protein-bound polysaccharides and electrophoretic migration of glycoproteins were studied in patients with various hematologic disorders. This series included 111 patients, divided as follows: acute leukemia, 15; chronic myelogenous leukemia, 4; chronic lymphocytic leukemia, 8; reticulum cell sarcoma, 3; lymphoma, 12; multiple myeloma, 5; mycosis fungoides, 2; infectious mononucleosis, 8; aplastic anemia, 2; polycythemia vera, 9; secondary polycythemia, 3; acute and chronic idiopathic thrombocytopenic purpura, 32; drug thrombocytopenic purpura, 4; acute and chronic anaphylactoid purpura, 4. Total protein-bound polysaccharides were determined with the method of Shetlar; migration of glycoproteins was studied with the method of Köiw. Normal values for protein-bound polysaccharides were 80–125 mg.%. Migration of glycoproteins of normal sera with the various protein fractions was as follows: albumin, 9.85%; α_1 globulin, 15.06%; α_2 globulin, 27.27%; β globulin, 33.00%; γ globulin, 14.52%.

A striking quantitative increase of total protein-bound polysaccharides was found in multiple myeloma; and significant increase in infectious mononucleosis, leukemias and lymphomas. Values in idiopathic thrombocytopenic purpura, drug purpura, anaphylactoid purpura and polycythemias were usually at the upper limits of normal or, occasionally, increased. Consistent changes in electrophoretic migration of glycoproteins were detected in few of the above disorders. Glycoproteins were found to migrate preferentially, bound to the following protein fractions: α_1 and α_2 globulins in lymphoma; the pathologic protein fraction in multiple myeloma; γ globulin in anaphylactoid purpura; albumin in idiopathic thrombocytopenic purpura and drug thrombocytopenic purpura. Acute types of idiopathic thrombocytopenic purpura also presented increase of γ globulin-bound carbohydrates. There was decrease of γ globulin-bound carbohydrates in infectious mononucleosis, which appeared of particular significance because of the increase in protein γ globulin fraction in these patients.

Thus, electrophoretic studies of glycoproteins appeared to be important in the diagnostic screening of some patients with hematologic diseases.

The Simultaneous Use of Chromium-Labeled Erythrocytes and I^{131}-Labeled Human Serum Albumin in Blood Volume Determinations

By *Clifford W. Gurney and Robert Bolt.* Department of Internal Medicine, University of Michigan, Ann Arbor.

Blood volume determinations employing iodoalbumin are falsely high because the peripheral hematocrit is greater than the total body hematocrit. Determination of the blood volume from the sum of the plasma volume and erythrocyte volume, each compartment being determined by separate tagging, eliminates this error.

Requiring only 3 vena punctures, blood is drawn for erythrocyte tagging just prior to injecting iodoalbumin; chromium-tagged blood is injected after removing a specimen for the plasma volume determination at 20 minutes; and, finally, blood is withdrawn at 40 minutes for erythrocyte volume determination.

Mechanical separation permits correction for the radiochromium in the plasma of the chromium-tagged blood injected, and radiochromium and radioiodine in the plasma of the final sample removed from the patient.

Blood volumes were determined in 15 patients suspected clinically of having increased or decreased blood volumes. In every instance, the sum of the plasma and erythrocyte volumes was less than the blood volume obtained from using iodoalbumin alone, and more than that obtained from using chromium-tagged erythrocytes alone. These results would be expected from any methods eliminating the incorrect assumption that peripheral hematocrit represents total body hematocrit. The ratio of total body hematocrit to peripheral hematocrit is somewhat less than previously reported, ranging between .62 and .92.

This method is more accurate than usual methods employed clinically. It requires less equipment than methods using dye for determination of

the plasma compartment, or beta emitters for tagging of erythrocytes. It is superior to using chromium alone for tagging both erythrocytes and plasma because it requires less time, and 3 rather than 7 vena punctures for each determination. For these reasons it has been found to be of value in clinical research where greatest accuracy is desired, and in selected patients where knowledge of erythrocyte volumes may influence therapy.

Simultaneous Estimation of Plasma Volume with Evans Blue Dye and I^{131}-Labeled Globulin

By *Gerald P. Rodnan*. Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

Plasma volume is commonly derived from the plasma dilution of Evans blue dye (T-1824) or iodinated albumin. In this estimation it is assumed that there has been complete mixing of the tagging material within the confines of the intravascular plasma compartment. In reality, both the dye (bound to plasma albumin) and the iodinated albumin are in dynamic equilibrium with a protein pool considerably larger than the plasma volume. Recent work by Walker and Ross suggests that the transcapillary exchange of globulin proceeds much more slowly than that of albumin. The present study was designed to compare values for plasma volume as obtained from dilution of Evans blue dye with those from a labeled globulin. Eighteen fasting subjects without disease likely to affect the plasma volume received immediately sequential injections of Evans blue dye and I^{131}-labeled human serum gamma globulin. The concentrations of dye and radioactivity were measured in plasma samples taken 10, 15, 20 and 30 minutes following injection. In every case the plasma volume estimated from the dilution of the globulin proved lower than that calculated from the dye. Utilizing levels extrapolated to "zero time," the mean plasma volume in this group was 2867 $\pm$ 409 ml. with the dye, and 2393 $\pm$ 328 ml. with the globulin, a difference of 16.5% ($p = <0.01$).

These findings suggest that there may be considerable transcapillary mixing of the dye (relative to globulin) even within the first minutes following injection. It is not unlikely that plasma volume estimated by various albumin-tagging methods will give erroneously high values. This may account for the impressions that total body hematocrit is less than large vessel hematocrit. The use of tagged globulin would appear to reduce this error.

Paper Electrophoresis in the Diagnosis of Myoglobinuria

By *G. R. Cooper, R. H. Owings, C. L. Whisnant and C. G. Cantrell*. Communicable Disease Center, Public Health Service, U. S. Department of Health, Education and Welfare; Department of Medicine, Emory University School of Medicine, and Grady Memorial Hospital, Atlanta.

The problem of proving the diagnosis of primary myoglobinuria was presented in a 24-year-old female Negro admitted to Grady Memorial Hospital with symptoms of myalgia, weakness and passage of dark urine. There was no evidence of anemia or hemolysis, but the urine gave a positive benzidine test. She developed acute renal insufficiency, and renal biopsy confirmed the suspicion of acute tubular necrosis. Recovery was prompt after diuresis began on the 14th day.

Attempts to demonstrate the presence of myoglobin in the urine were made with the spectrophotometer, paper electrophoresis and ultracentrifuge. Spectrophotometric curves indicated that either myoglobin or hemoglobin was present. Paper electrophoresis, using bromphenol blue stain, revealed that a mixture of serum proteins was also present in the urine. Ultracentrifugation of the urine concentrate gave a sedimentation constant compatible with myoglobin, but a control from a patient with myotonia also gave similar results. However, a heme compound was not present in the latter urine.

The above evidence was considered compatible with the clinical diagnosis of myoglobinuria, but did not constitute proof.

A specific analytic procedure was devised, and found applicable to the patient's urine. One part of a benzidine-positive urine is added to 2 parts of human serum. The mixture is separated by paper electrophoresis and stained with a hydrogen peroxide-benzidine spray. The serum proteins prevent adsorption of myoglobin or hemoglobin, but do not stain. Myoglobin migrates only half the distance of hemoglobin; thus, easy differentiation is possible. Myoglobin prepared from rabbit muscle has a different mobility than that from human muscle and heart.

It was concluded that paper electrophoresis with specific staining provides laboratory confirmation of the clinical diagnosis of myoglobinuria.

BLOOD PROTEINS

Lipoproteins Determined by Starch Electrophoresis in Idiopathic Hyperlipemia and in Idiopathic Hypercholesteremia

By *Fiorenzo Paronetto, Chun-I Wang and David Adlersberg.* Departments of Medicine and Chemistry, Mount Sinai Hospital, New York City.

Cholesterol (total and free) and phospholipid determinations were performed after starch electrophoresis of human serum. With the aid of simultaneous protein analyses, 3 distinct lipoprotein fractions were identified: α_1, α_2 and β. The study included 10 persons: 3 normal controls, age 25–33 (group A); 4 with idiopathic hyperlipemia, age 38–48 (group B) and 3 with idiopathic hypercholesteremia, age 32–57 (group C). In group A, the serum lipid levels were 226, 169, 286 and 640 mg.% for total cholesterol, esterified cholesterol, phospholipid and total lipids, respectively. In group B, the corresponding serum lipid levels were 528, 367, 527 and 2263 mg.%, respectively. In group C, the levels were 350, 264, 354 and 1010 mg.%, respectively. The distribution of cholesterol in the lipoprotein fractions in group A was 30.5% in α_1, 4.8% in α_2 and 64.7% in β; that of phospholipid was 50.0, 3.1 and 46.9%. In group B, the distribution of cholesterol was 8.2% in α_1, 32% in α_2 and 59.8% in β lipoprotein; that of phospholipid was 21.3, 25.1 and 53.6%. In group C, the distribution of cholesterol was 11.2% in α_1, 5.5% in α_2 and 84.0% in β lipoprotein; that of phospholipid was 22.5, 12.8 and 64.7%. In group A, the cholesterol:phospholipid ratio was 0.58 in α_1, 2.2 in α_2 and 1.35 in β lipoprotein. In group B, the corresponding ratios were 0.35 in α_1, 1.26 in α_2 and 1.08 in β lipoprotein; in group C, the ratios were 0.52 in α_1, 0.51 in α_2 and 1.48 in β lipoprotein. The recovery of lipid from the starch segments amounted to an average of 85% for cholesterol and to 79% for phospholipid.

These studies revealed marked differences in lipoprotein patterns between paper and starch electrophoresis because the adsorption of lipoprotein at the point of origin appeared to be an important interfering factor in the former procedure. Using starch electrophoresis, idiopathic hyperlipemia is characterized by marked elevation of the α_2 lipoprotein fraction, whereas in idiopathic hypercholesteremia considerable elevation of the β lipoprotein fraction is seen. In both metabolic errors, there is a marked reduction of α_1 lipoprotein.

The In-Vitro Effect of Soy Bean Phosphatides on Serum Lipoproteins of Normal and Hyperlipemic Subjects

By *Bernard A. Sachs and Ethel Danielson.* Medical Division, Montefiore Hospital, New York City

A purified extract of natural soy bean phosphatides containing approximately equal amounts of lecithin, cephalin and lipositol was mixed with the postabsorptive sera of 6 normal and 5 hyperlipemic subjects and analyzed for protein and lipid by paper electrophoresis. An aliquot of each mixture was incubated at 37° for 24 hours and again subjected to electrophoretic analysis. The nonincubated sera demonstrated little or no change when compared to the phosphatide-free controls. However, all of the phosphatide-containing incubated sera, both normal and hyperlipemic, showed an increase in the migration velocity of β lipoprotein, i.e., lipoprotein associated with β globulin migrated to the region between α_2 and α_1 globulin. In addition, 5 of the 6 normal sera and 1 of the 5 hyperlipemic sera demonstrated a definite but milder increase in migration velocity of the lipid-staining band associated with α_1 globulin and albumin (α lipoprotein) to an area on the strip immediately beyond albumin.

To evaluate further the "lipoprotein shift" observed, the alcohol soluble fraction of the soy bean phosphatide containing approximately $\frac{2}{3}$ lecithin and $\frac{1}{3}$ cephalin, and the alcohol insoluble fraction containing approximately $\frac{2}{3}$ lipositol and $\frac{1}{3}$ cephalin, were tested in a similar manner with the sera of 10 normal and 5 hyperlipemic subjects. After incubation, the alcohol soluble fraction produced little or no change in the serum lipoproteins. However, the alcohol insoluble fraction produced an increase in migration velocity similar to that demonstrated with the whole soy bean phosphatide complex. It is believed that lipositol is the compound responsible for the changes observed. These changes in the migration velocities of the serum lipoproteins produced by soy bean phosphatides are similar to those produced by heparin in vivo and "clearing factor" in vitro.

Detection of Protein-Bound Polysaccharides on Electropapergrams of Serum

By *William Q. Wolfson and Irvin I. Young.* Office of the Regimental Surgeon, Headquarters 18th Infantry Regiment and the Department of Medicine and Laboratory Service, U. S. Army Hospital, Fort Riley, Kansas; and the Metabolic Research unit, Department of Medicine, Wayne University College of Medicine and City of Detroit Receiving Hospital.

Sera were submitted to electrophoresis on Munktell 20-B paper in pH 8.6 veronal or Michaelis buffer with 10% added ethanol. One portion of the strip was stained with bromphenol blue for protein and a second portion stained for "protein-bound polysaccharide" by one of the reported technics: (1) periodate oxidation followed by Schiff's leukofuchsin or (2) toluidine blue after treatment with cold or hot bromine water. Periodate-Schiff staining was unreproducible to the point of being meaningless. Patterns showed little regularity except for a tendency to maximum staining among α globulins;

there was no resemblance to the bromphenol blue pattern. Without prior bromine treatment, toluidine blue did not stain. After cold bromine, there was moderate metachromatic staining which was much more intense after hot bromine water. This stain was highly reproducible but the location and relative intensity of the bands very closely paralleled the protein bands revealed by bromphenol blue rather than the known distribution of polysaccharides among serum proteins.

Since the stains give entirely different patterns, only one or neither can be considered a selective stain for polysaccharide. Since the periodate-Schiff stain is nonreproducible and the bromine-toluidine blue appears to stain some universal component of protein, it is not likely that, when applied to this type of sample, either stain is a valid reagent for the detection of protein-bound polysaccharide.

The Intravenous Administration of Large Doses of Immune Globulin to Human Subjects

By *Avery A. Sandberg, George E. Moore, Merrill Bender and Robert Tarail.* Roswell Park Memorial Institute, Buffalo, New York.

In contrast to albumin, the effects of the intravenous administration of immune globulin have not been intensively investigated because of alleged toxicity. The purpose of the present study was to evaluate certain effects of such administration. Over 120 infusions of large doses (up to 100 Gm. per injection) of immune globulin were given to 15 subjects; 14 with malignancies and 1 with agammaglobulinemia. The largest total amount given was 530 Gm. Commercially available "poliomyelitis immune globulin" was diluted with 0.25–1.0 L. isotonic saline or 5% glucose and given intravenously over periods of 0.3–6 hours. Sudden and severe reactions were observed in 3 patients, consisting of peculiar collapse (transient unresponsiveness, flushed skin, difficulty in breathing and phonation, severe backache) without changes in blood pressure, electrocardiogram or pulse. The patients recovered quickly and later received large doses without such reactions. Even though most patients developed occasional symptoms, either during or after the administration of many large doses of γ globulin, they were not sufficiently severe to interfere with continued administration.

No significant differences were observed in the plasma clearance rate of I^{131}-labeled immune globulin in 2 patients, before and after the administration of large doses. In the agammaglobulinemic patient the concentration of γ globulin (determined electrophoretically) was raised from zero to 27% of total serum proteins and significant concentrations (5%) were present 20 days following the infusions. The ultrafiltrability of sodium, potassium and chloride in blood serum did not appear to be affected by large doses of γ globulin in 2 patients.

Irrespective of the fact that present preparations may produce alarming reactions, the feasibility of administering large doses of γ globulin intravenously appears to be far greater than has hitherto been recognized. This finding may be of significance whenever therapy with γ globulin is required, as in agammaglobulinemia.

A Study of Hexosamine Content of Serum Globulins

By *Alfred J. Bollet.* Wayne University College of Medicine, Detroit

The hexosamine content of serum globulin fractions was studied in several diseases. In normals the perchloric acid soluble mucoprotein fraction (PSM) was found to contain 4.35 ± 0.27 mg.% (s.e.m.) of hexosamine; the amount of hexosamine was 7.3% ± 0.4% of the amount of protein found in the PSM by the biuret method (casein standard). In 15 patients with active rheumatoid arthritis the PSM contained 11.5 ± 1.61 mg.% hexosamine, which was 11.2 ± 0.8% of the protein. Similar changes were found in patients with pneumonia, systemic lupus erythematosus, rheumatic fever and acute gouty arthritis. With suppression of the acute inflammatory process, the hexosamine content of the PSM fell, as did the ratio of hexosamine to protein.

The hexosamine content of each of the electrophoretic globulin fractions was measured after separation on filter paper. Normal sera averaged 19 mg.% hexosamine in the α_1 fraction, 25 mg.% in α_2, 16 mg.% in β and 24 mg.% in γ. Abnormal sera showed considerable elevations of hexosamine content of α_1 and α_2 globulins in acutely ill patients with a variety of diseases, while there were minimal changes in β, and inconstant changes in γ globulin hexosamine. The relative hexosamine content of the α_1 globulin increased from the normal average of about 4 to 6–8% in most acutely ill patients. No such change in the ratio of hexosamine to protein was observed in the other globulin fractions, where increases in hexosamine were accompanied by similar increases in the amount of protein. The PSM has been shown to be an α_1 globulin by Winzler, but observed alterations in the PSM protein and hexosamine components could not account for all the changes observed in the α_1 fraction. No changes specific for any of the connective tissue diseases were noted.

The Clinical Significance of Hyperglobulinemia

By *Alvan R. Feinstein and Robert Petersdorf.* Department of Medicine, Yale University, New Haven.

In order to ascertain the significance of the isolated laboratory finding of elevation of the serum globulin, the hospital records of 394 patients with serum globulin levels of 3.9 Gm.% or higher (upper limit of normal by the method of Cohn and Wolf-

son) were analyzed. Of these, 268 patients were found to have diseases in which hyperglobulinemia had been frequently reported (multiple myeloma, "collagen" disease, cirrhosis and other diseases of the liver, chronic pulmonary diseases and certain chronic infections). On the other hand, the remaining 126 patients manifested a wide variety of disorders not commonly associated with abnormally high serum globulin levels, including diseases of the cardiovascular, renal, endocrine and musculoskeletal systems. However, no patient without significant organic disease exhibited this abnormality.

A further breakdown of the cases according to the degree of serum globulin elevation revealed that of 60 patients with levels of 5.0 Gm.% or higher, 30 had multiple myeloma, sarcoid or collagen diseases and all but 5 in this group had other diseases commonly associated with hyperglobulinemia. In a second group of 168 patients whose globulin levels fell between 4.2 and 5.0 Gm.%, the majority were diagnosed as having liver disease, metastatic malignancy and chronic pulmonary difficulties, whereas only a few had multiple myeloma, collagen disease or sarcoid. In contrast, amost 50% of patients with borderline elevation of the serum globulin (less than 4.2 Gm.%) manifested a great variety of chronic diseases involving one or several organ systems. These data suggest that a slightly elevated serum globulin level is of limited diagnostic significance.

Zinc Sulfate Turbidity as a Measure of the Serum Gamma Globulin

By *Thomas E. Wilson, Charles H. Brown and Adrian Hainline, Jr.*

To determine the accuracy of the zinc sulfate turbidity test (ZST) as a measure of the level of serum γ globulin, the results as expressed in units were compared with the Tiselius electrophoretic protein patterns in 174 cases. When compared with the γ globulin levels, a correlation coefficient of 0.59 was obtained. The correlation of 0.59 indicates that the zinc sulfate closely parallels the level of γ globulin. Because it has been reported that factors other than γ globulin affect the zinc sulfate turbidity, it was compared with the other fractions of the electrophoretic pattern. When zinc sulfate turbidity was compared with the albumin, α and β globulins no correlation was obtained. The zinc sulfate turbidity was then compared with the total serum globulin in 273 cases as determined by the method of Pillemer and Hutchinson, and a correlation coefficient of 0.39 was obtained. This indicates that the γ globulin is the principal factor effecting the zinc sulfate turbidity. It has been reported that the addition of albumin to serum with high γ globulin levels decreases the amount of globulin precipitated, thus lowering the zinc sulfate turbidity results. For this reason the zinc sulfate turbidity was compared with the albumin-γ globulin ratio in 165 cases and a correlation of 0.63 was obtained, suggesting that the zinc sulfate turbidity is affected by changes in the albumin-γ globulin ratio as well as by changes in the γ globulin alone.

Properdin Levels in Human Disease

By *Carl F. Hinz, Jr. and John R. Murphy.* Western Reserve University, School of Medicine, Cleveland.

Properdin, a naturally occurring serum protein, combines in vitro with certain high molecular weight polysaccharide complexes. Properdin is essential for certain viricidal, bactericidal and hemolytic properties of normal human serum. In experimental animals low properdin levels have been observed following shock, radiation and experimental infection, conditions in which death has been attributed to bacteremia or endotoxemia. Accordingly, there has been interest in the properdin levels in human disease, particularly in infections.

The current observations indicate that the properdin level in normal persons remains constant; bears no relation to age, sex, or leukocyte count; and is unaffected by "stress" and radiotherapy. Others have observed no effect following anesthesia and surgery, including splenectomy.

A fall in properdin level has been observed during the acute phase of Gram-negative bacterial infections, including pyelonephritis, meningococcemia, H. influenzae meningitis and bacillary dysentery; and in some patients with pneumococcal pneumonia. It is of interest that in vitro properdin combines with the cell walls or endotoxin from Gram-negative organisms and with certain pneumococcal polysaccharides. The properdin level usually has returned to normal during the first week of convalescence, and no subsequent rise above normal levels has been observed. In other infections, properdin titers have remained normal. Clinical states which are associated with a susceptibility to infection, and in which properdin levels have been normal during infection-free periods, include agammaglobulinemia, cirrhosis, bronchiectasis, unexplained recurrent infection, acute leukemia and steroid therapy.

Low properdin levels have been repeatedly observed in a patient with paroxysmal nocturnal hemoglobinuria, the one disorder in which there has been demonstrated a relationship in vitro of properdin to hemolytic mechanism.

Thus, patients with diseases caused by bacteria or abnormal cells known to interact with the properdin system in vitro may have low serum properdin levels.

CARDIOVASCULAR SYSTEM

Observations on Vascular Sounds: The "Pistol-Shot" Sound, and the Korotkoff Sound

By *Ramon L. Lange, Robert P. Carlisle and Hans H. Hecht.* Department of Medicine, University of Utah College of Medicine, Salt Lake City.

Certain clinical observations suggest that the genesis of spontaneous "pistol-shot" and the induced Korotkoff sounds may be similar. The time relationships of sound and pressure phenomena were studied: (1) in vessels exhibiting spontaneous sounds, and (2) distal to standard blood pressure cuffs during the appearance of Korotkoff sounds using an electromanometer-arterial needle system and a microphone. The signal outputs were recorded from a twin-beam oscilloscope using high film speed. The phenomena were studied in patients with aortic insufficiency, thyrotoxicosis, and in normal subjects both at rest and after the occurrence of "spontaneous" sounds induced by hypoxia with and without vasodilators.

Spontaneous sounds of low frequency and brief duration have been recorded from all peripheral vessels. They are of the same character as the induced Korotkoff sounds. Simultaneous pressure-sound records consistently revealed that both types of sound appeared *before* the pressure rise at any given point. The sound disappeared either before the pressure pulse arrival or early on the anacrotic rise.

This relationship of sound and pressure cannot be explained by existing theories. "Spontaneous" sounds were present or could be produced when: (a) flow rates were high, (b) the absolute value and rate of anacrotic pressure rise was high, (c) there was no significant degenerative vascular disease (normal arterial distensibility). Assuming laminar flow to be stable in both systole and diastole, it can be shown that the acceleration of the slow-moving lamina of the diastolic pattern by the lamina with near maximal velocity in the systolic pattern is a function of the above conditions. This acceleration would add energy rapidly to the late diastolic portion and would temporarily disrupt quiet, nonturbulent flow with quick reversion to quiet flow soon after the onset of systole. A similar situation occurs during the production of Korotkoff sounds which may be nearly identical in character to spontaneous sounds.

Clinical and Physiologic Studies in Ebstein's Malformation*

By *George H. Reifenstein, R. Maurice Hood and Raymond H. Watten.* Cardiorespiratory Unit, U. S. Naval Hospital, Oakland, California.

Criteria for establishing the diagnosis of Ebstein's malformation of the tricuspid valve are late or absent cyanosis, roentgenographic evidence of right atrial and right ventricular enlargement without signs of pulmonary vascular congestion and data obtained from cardiac catheterization.

Clinical, roentgenologic and physiologic studies have been obtained on 2 young men who were not cyanotic and had minimal cardiac disability. One, a 16-year-old boy, had been previously diagnosed as having rheumatic mitral disease. The other, a 20-year-old Marine, was under observation for a noncardiac condition. Cardiac catheterization was done because of a grossly enlarged heart. No cardiac murmurs were present in the second case.

The hemodynamic data obtained were similar in both cases. Normal pressures were recorded in the right ventricle and pulmonary artery, while moderately elevated pressures were found in the right atrium. Arterial oxygen desaturation and increased oxygen capacity indicating a right to left shunt were found in 1 case. Oxygen content was normal in the second case.

Diagnostic criteria for Ebstein's malformation were fulfilled in these 2 cases which illustrate the value of right heart catheterization in suspected congenital cardiac lesions.

Hemodynamic Observations in Eisenmenger's Syndrome

By *Hiroshi Kuida, Paul Novack, Leonard A. Cobb, Florence W. Haynes and Lewis Dexter.* Department of Medicine, Peter Bent Brigham Hospital, and Harvard Medical School, Boston.

Eisenmenger's syndrome is a poorly defined term applying to an anatomically dissimilar group of congenital cardiac anomalies. Criteria necessary for establishing this diagnosis by cardiac catheterization vary from laboratory to laboratory. In our laboratory the term is used to designate any condition in which both ventricles and aorta and pulmonary artery are demonstrated to be in free communication at the ventricular or arterial level, irrespective of the presence, magnitude or direction of shunts. By this definition, Eisenmenger's syndrome would include patients with a large ventricular septal defect, cor triloculare biatriatum, the true Eisenmenger's complex, common truncus arteriosus, large aortic-pulmonary fenestration, and a large patent ductus arteriosus, all of which tend to have similar clinical courses and manifestations.

Physiologically, systolic pressures in both ventricles, aorta and pulmonary artery are identical, beat for beat, over a wide range of variation in pressure produced by exercise, Valsalva maneuver, or any method by which the pulmonary or systemic resistance can be differentially altered. In patent ductus arteriosus (and presumably in large aortic

* The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

septal defects) not only are systolic pressures identical under these circumstances, but mean and diastolic pressures as well. This has not been observed in those with free communication at the ventricular level.

In similarly located but small defects, and other congenital or acquired conditions with pulmonary hypertension (atrial septal defect, mitral stenosis, primary pulmonary hypertension, etc.), the systolic pressures in the pulmonary artery and aorta may fortuitously be the same at rest, but will diverge on altering the resistance in the greater or lesser circulation by exercise, etc.

In Eisenmenger's syndrome, pulmonary hypertension is judged to be a direct consequence of the free communication between the systemic and pulmonary circuits. Survival and longevity in these cases, therefore, is dependent on an increased pulmonary vascular resistance persisting from birth. Pulmonary hypertension in the other conditions mentioned is variable in degree and is a secondary consequence of factors as yet poorly understood.

Diagnosis of the Ostium Primum Defect

By *A. Calhoun Witham and Robert G. Ellison.* Departments of Medicine (Cardiology) and Surgery (Thoracic) and Georgia Heart Association Laboratory for Cardiovascular Research, Medical College of Georgia, Augusta.

Seven to 20% of defects of the atrial septum are in the ostium primum region, may extend into the membranous ventricular septum, and are almost always associated with a defective mitral or common AV valve (complete or incomplete persistence of the AV canal). Surgical closure has been unsatisfactory and should probably be attempted only under direct vision. Consequently, preoperative diagnosis is of considerable practical importance. Four, probably 5, such cases have been subjected to extensive clinical study. All were female. Cyanosis was absent to moderate. Congestive failure may occur in childhood, although our oldest example is now 34. When the mitral valve is incompetent, a distinctive syndrome results. This is almost always the case with the congenitally cleft mitral valve, but the common AV valve is sometimes competent. Auscultation reveals a parasternal systolic murmur of variable intensity, often very loud, a split P-2, an apical systolic murmur of mitral regurgitation, and a low pitched diastolic rumble between apex and sternum. Phonocardiography may be extremely helpful in differentiating Lutembacher's syndrome, and in 4 instances has verified a remarkably soft mitral first sound with normal appearance time relative to the ECG. Fluoroscopy revealed pulmonary plethora, often hilar dance, biventricular and right or left atrial enlargement. ECG's showed incomplete right bundle branch block, first degree A-V block and, occasionally, evidence of left ventricular hypertrophy. Catheterization data indicated a pulmonary flow 3 to 4 times the systemic flow in all except the single case with severe pulmonary hypertension. The catheter took a course apparently diagnostic of persistent A-V canal in 1 instance, entering the left ventricle directly from the right auricle and, upon withdrawal, retreating through the right ventricle.

Hypertrophy of the Crista Supraventricularis: A Revised Concept of the Electrocardiographic Findings in Atrial Septal Defect

By *S. Gilbert Blount, Jr., E. A. Munyan and Murray S. Hoffman.* University of Colorado Medical Center, Denver.

Because of a growing dissatisfaction with the concept of incomplete right bundle branch block as an explanation for the electrocardiographic findings in atrial septal defects, a study was conducted to determine: (1) the frequency of the rSr′ pattern in right-sided leads in normal children, and (2) the possible mechanisms involved in the similar though exaggerated pattern seen in certain congenital and acquired cardiac defects.

Multiple right and left anterior electrocardiographic leads were taken on 50 normal subjects. They were taken from V_6R to V_6, and 1, 2, 3 and sometimes 4 intercostal spaces above V_6R to V_6. In 49 of the 50 subjects, all of whom had a normal QRS time, an rSr′ pattern was demonstrated in at least 1 of the right-sided leads taken. It is felt that this rSr′ pattern represents the 3 normal vectors in ventricular depolarization—septum, free wall and crista supraventricularis.

Intracardiac electrocardiographic studies were performed on patients with atrial septal defects. These studies showed a splintered complex of the delayed R wave variety from the right ventricular outflow tract, the inflow tract showing an rS pattern. This correlated well with direct epicardial leads taken from the surface of the right ventricle at the time of surgery on patients with atrial septal defects. These latter studies revealed an rsR′ or an rsRs′ pattern originating from the so-called "crista" area and an RS pattern originating from the remainder of the right ventricle.

Clinical experience with mitral stenosis and valvular pulmonic stenosis has revealed the rSr′ pattern to be an early stage in the development of the Rs or qR pattern of right ventricular hypertrophy.

If the rSr′ pattern seen in these cases were due to right bundle branch block, one would expect the pattern to be present over the entire right ventricle rather than in a localized area in the right ventricular outflow tract. It is concluded that the rSr′ pattern seen in atrial defects is not due to incomplete right bundle branch block but rather to hypertrophy of the crista supraventricularis, and repre-

sents simply an exaggeration of the normal crista vector seen in normal children.

Lesser Circulation Dynamics before and after Closure of Atrial Septal Defects

By *Fouad Bashour and Paul Winchell*

Fourteen adult patients were studied before and after closure of atrial septal defects. In 1 case mitral valvular disease was found at surgery.

Physiologic studies were done as early as 3 months and as late as 61 months following surgical repair. In 2 cases a small left-to-right shunt persisted.

The important findings include a marked decrease in pulmonary blood flow, pulmonary arterial oxygen saturation and right ventricular work. Pulmonary vascular resistance increased after closure, while no significant change in oxygen consumption was noted. In each instance, marked clinical improvement occurred.

The Hemodynamics of Experimentally-Produced Isolated and Combined Lesions of the Mitral Valve

By *Howard L. Moscovitz and Robert J. Wilder*. Departments of Medicine and Surgery, The Mount Sinai Hospital, New York City.

Simultaneous pressure curves were recorded at equal sensitivities from the left atrium, left ventricle and aorta of 39 dogs in whom mitral valve lesions had been acutely produced. Pressure pulses were obtained by direct needle puncture of the cardiac chambers and recorded by means of 3 matched strain gages on a 4-channel oscillograph, together with an electrocardiographic lead.

Isolated mitral insufficiency was created by tearing part of the posterior mitral leaflet and its chordae tendineae with a nerve hook. The left atrial pressure tracing demonstrated increased prominence of the late systolic v wave which began its ascent earlier and grew progressively taller as the insufficiency was magnified. The slope of the isometric contraction phase of the left ventricle did not change appreciably until the mitral reflux was made massive enough to cause shock and left ventricular failure. Aortic root compression caused marked increase in left atrial pressure in dogs with incompetent mitral valves.

Isolated mitral stenosis, produced by a constricting suture encircling the mitral annulus, was characterized by increase in height and width of the a wave of atrial contraction and the appearance of an elevated left atrioventricular filling pressure gradient. The left ventricular end-diastolic pressure fell in response to the acute restriction of mitral flow. When atrial fibrillation was produced in a dog with mitral stenosis, the contour of the left atrial curve resembled a plateau.

In combined mitral stenosis and insufficiency, the effect of superimposed stenosis was to markedly reduce the left atrial pulse pressure and obscure the prominence of the late systolic v wave of mitral insufficiency. Despite the camouflage of the pressure characteristics of mitral regurgitation in dogs with this combined lesion, significant mitral reflux still occurred, as demonstrated by direct injection of radiopaque medium into the left ventricular chamber by retrograde arterial catheter.

Angiocardiographic and Physiologic Correlations in Mitral Valvular Disease

By *Peter R. Mahrer, Daniel S. Lukas and Israel Steinberg*. Department of Medicine, and Cardio-Pulmonary Laboratory, New York Hospital-Cornell Medical Center, New York. (Aided by a grant from the National Heart Institute.)

To relate the anatomic to the physiologic abnormalities in mitral stenosis, the size of the left atrium and pulmonary artery, as defined by angiocardiography, was compared to hemodynamic data obtained by cardiac catheterization. Fifty-one patients with mitral stenosis (MS) and 5 with mitral insufficiency (MI) were studied. In 47 of the MS group and 3 of the MI group the diagnosis was confirmed during mitral valvuloplasty.

The cross-sectional area of the main pulmonary artery correlated well with the mean resting pulmonary arterial pressure ($r = 0.657$). A low-grade relationship ($r = 0.308$) existed between this area and the pulmonary vascular resistance. The area varied inversely ($r = -0.470$) with the calculated size of the mitral valve orifice.

In MS there was no correlation between the size of the mitral orifice and the planimetrically-determined area of the opacified left atrium, or the atrial size and the pulmonary arterial cross-sectional area. This lack of correlation was noted also in a subgroup of patients with pure mitral stenosis selected by the most stringent criteria. A low-grade inverse correlation ($r = -0.343$) existed between the index of atrial size and the cardiac index. The left atrium was significantly larger in atrial fibrillation than in NSR. The mean left atrial size in MI was twice that in MS.

Definite correlations exist between the anatomic and physiologic abnormalities, but the degree of correlation is generally such that other factors, not accounted for in this study, must play a significant part in influencing alterations in structure.

The Pulmonary Blood Volume and Pulmonary Hematocrit in Mitral Stenosis

By *Eliot Rapaport, Hiroshi Kuida, Florence W. Haynes and Lewis Dexter*. Departments of Medicine, V. A. Hospital and Albany Medical College, and the Peter Bent Brigham Hospital and Harvard Medical School, Boston.

The Stewart-Hamilton and Bradley methods for "pulmonary" blood volume determination were simultaneously studied during right heart catheterization in 17 patients with mitral stenosis utilizing Cr^{51}-tagged red cells and T-1824.

"Pulmonary" volumes ranged from 595 cc./M.² to 1411 cc./M.² by the Stewart-Hamilton and 422 cc./M.² to 1206 cc./M.² by the Bradley methods. Expressed as percentage of "pulmonary" to total blood volume, values ranged from 23.2 to 40.1% by the former and 17.1 to 42.7% by the latter method. Cardiomegaly and secondary pulmonary vascular disease, as well as the severity of mitral stenosis, appeared to influence the volumes obtained. Thus, although a number of individual patients did demonstrate an increased "pulmonary" volume, a poor correlation was found between mitral valve area or "pulmonary capillary" pressure and the "pulmonary" blood volume.

A good correlation was seen between individual volumes calculated by the Bradley and the traditional Stewart-Hamilton methods ($r = +.82$, $p < .01$). The results indicate that with careful analytic technic the Bradley method can be satisfactorily applied to measurement of "pulmonary" blood volume. It may prove the preferable method in situations where cardiac output is materially reduced or pulmonary volume increased. Under these circumstances, the indicator dilution curve exponential downstroke may be so gradual that extrapolation fails to separate accurately the effects of recirculation.

Average mean transit time was shorter for cells than for dye in all patients (mean ratio .95, s.d. .03). This resulted in a lower "pulmonary" compared to large vessel hematocrit by the Stewart-Hamilton technic. The mean ratio of "pulmonary" to large vessel hematocrits by the Bradley method was .91 ($p < .01$). Since both methods measure predominantly large vessel compared to actual capillary blood, the hematocrit of the pulmonary capillary bed itself must be considerably less, and contributes to over-all lowering of total body compared to large vessel hematocrit.

Central Aortic and Femoral Pressure Pulses in Aortic Valve Disease

By *Joseph Roshe, J. Alex Haller, Jr. and Andrew G. Morrow.* Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

Simultaneous central aortic and femoral arterial pressure pulses were studied in 25 patients: 5 had normal aortic valves, 7 aortic insufficiency, 7 aortic stenosis, and 6 aortic stenosis and insufficiency. After percutaneously introducing a 13 gage needle into the right femoral artery, a #6 Cournand catheter was passed through the needle into the ascending aorta and its tip positioned above the aortic valve. A #18 Cournand needle was placed in the left femoral artery and simultaneous central and femoral pressure pulses recorded with P23A strain-gages connected to either a photographic or direct writing recorder.

Central pulse pressures and femoral/central pulse pressure ratios averaged 46 mm. Hg, and 1.48 in patients with normal aortic valves; 80 mm. Hg, and 1.73 in aortic insufficiency; 41 mm. Hg, and 1.47 in aortic stenosis; and 84 mm. Hg, and 1.34 in aortic stenosis and insufficiency.

The contour of the central pressure pulse in aortic stenosis exhibited one or more sharp notches low on the anacrotic limb; the initial shoulder was delayed, and maximum ejection prolonged. The femoral pressure pulse had a flat or rounded summit which was sometimes slurred. Combined aortic stenosis and insufficiency was characterized centrally by an anacrotic notch or vibration, and a wide pulse pressure; the femoral pressure pulse was collapsing, and had a double-peaked (bisferiens) or slurred summit. Femoral maximum ejection comprised 44% of total ejection in patients with normal aortic valves, 30% in aortic insufficiency, 59% in aortic stenosis, and 36% in aortic stenosis and insufficiency. Centrally, the duration between onset of ejection and the anacrotic shoulder averaged 35% of total ejection with normal aortic valves, 46% in aortic insufficiency, 58% in aortic stenosis, and 62% in aortic stenosis and insufficiency.

Such an analysis of pressure pulse contours has proved useful in the differential diagnosis of aortic valve disease.

Left Heart Catheterization in Aortic Stenosis

By *Paul Novack, Leonard A. Cobb, Hiroshi Kuida, Florence W. Haynes and Lewis Dexter.* Departments of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

The increasing number of patients undergoing surgery for the relief of aortic stenosis makes desirable a method by which patients with this lesion can be evaluated, both from the point of view of preoperative severity and postoperative improvement. The introduction of left heart catheterization and the inadequacy, in our experience, of pressures taken at the time of operation prompted the study here presented.

Ten left heart catheterizations were performed on 6 patients with clinically pure aortic stenosis. Pressures were recorded from the left ventricle and left atrium through a polyethylene catheter and from a brachial artery needle. Cardiac output was determined by the indicator dilution method. Mean systolic pressure gradient (in mm. Hg) across the aortic valve was determined by planimetric integration of simultaneous left ventricular and brachial artery pressure pulses. Stenotic valve areas (in cm.²) were calculated by the Gorlin formula.

Five of the 6 patients underwent aortic valvuloplasty. Two of these had satisfactory pre- and postoperative studies. Aortic valve mean systolic pressure gradients and calculated valve areas, respectively, were 85 and 93 mm. Hg and 0.5 and 0.6 cm.^{2} before, and 54 and 50, and 0.6 and 0.8 after operation. One patient, who preoperatively had a gradient of 95 and a valve area of 0.4, died during operation. Two patients had unsatisfactory preoperative studies, but following surgery had gradients of 22 and 39 and areas calculating 1.0 and 0.9, respectively. Operation was deferred on the sixth case, who had a gradient of 70 and a 0.7 valve area. Of particular interest was the fact that cardiac output was maintained at normal levels in these patients, averaging 3.9 L./min./M.^{2} (range 3.3 to 4.9).

These studies indicate the importance of determining the flow as well as the pressure gradient across the valve in assessing the severity of stenosis.

The Hemodynamic Diagnosis of Tricuspid Stenosis

By *Thomas Killip, III and Daniel S. Lukas.* Department of Medicine and Cardio-Pulmonary Laboratory, New York Hospital–Cornell Medical Center, New York. (Aided by a grant from the National Heart Institute.)

Reliable hemodynamic criteria for the diagnosis of tricuspid stenosis have not been established.

The mean pressure gradient during ventricular diastole, when blood flows across the tricuspid valve, was determined from right atrial and ventricular pressures recorded through a cardiac catheter. In 12 control patients with rheumatic heart disease, proved at autopsy not to have tricuspid stenosis, the gradient at rest was -0.03 ± 1.1 mm. Hg.

A significant gradient ranging from 2.9 to 13.4 mm. Hg was present in 10 patients with tricuspid stenosis. The diagnosis was suspected clinically in 9, and in 1 was made hemodynamically and confirmed at autopsy. The invariable increase in gradient with exercise provided a valuable test when the pressure difference at rest was small. The largest gradients occurred in combined stenosis and insufficiency. In sinus rhythm the gradient was most striking during atrial systole. In atrial fibrillation it was greatest during early ventricular diastole. These differences were reflected in the auscultatory findings.

The pressure in the right atrium at the end of ventricular diastole (Z-point) was higher than the corresponding ventricular pressure in every patient with tricuspid stenosis, but did not provide an index of the mean diastolic gradient. In 4, the difference was no greater than noted in the control series.

Although resting gradients generally were small, calculated tricuspid orifice area was less than 1.5 cm.^{2} in 9 cases. In 2 patients the estimated orifice was confirmed during tricuspid valvuloplasty. One of these had isolated, pure tricuspid stenosis, a resting gradient of 4.7 mm. Hg and a calculated orifice of 1.1 cm.^{2}

The diagnosis of tricuspid stenosis can be made accurately from hemodynamic data if proper emphasis is placed upon the mean pressure gradient between right atrium and ventricle *throughout* ventricular diastole.

Clinical and Physiologic Aspects of Tricuspid Stenosis

By *Thomas Killip, III and Daniel S. Lukas.* Department of Medicine and Cardio-Pulmonary Laboratory, New York Hospital–Cornell Medical Center, New York. (Aided by a grant from the National Heart Institute.)

Ten patients with tricuspid stenosis were studied by cardiac catheterization. In one the lesion was isolated. Four had combined mitral and tricuspid stenosis and the rest had multivalvular disease. A rumbling tricuspid diastolic murmur, loudest parasternally in the 4th and 5th left intercostal spaces and increased in intensity by inspiration, was present in 9.

Mean right atrial pressure was elevated to levels of 6 to 21 mm. Hg and was highest in patients with associated tricuspid insufficiency or right ventricular failure. During exercise atrial pressure rose to 7 to 29 mm. Hg. Right atrial hypertension was reflected clinically by marked enlargement of the atrium, tall P-waves in the EKG and hepatomegaly. Venous distension was not invariably present and depended on the height of the atrial pressure. Presystolic pulsations in the neck veins and liver were not always present in patients with sinus rhythm despite vigorous contraction waves in the right atrium. Edema and ascites were prominent only in those with severe multivalvular disease, and did not depend on the size of the tricuspid orifice.

The hemodynamic disturbances and associated symptoms varied with the presence and severity of associated valvular disease. In the patient with isolated tricuspid stenosis, pulmonary vascular pressures were normal and dyspnea was not prominent. Cardiac output was only 1.9 L./min./M.^{2} at rest, and 2.1 during exercise. In patients with associated mitral stenosis, cardiac output, pulmonary vascular pressures and resistance were lower than in patients with a similar grade of isolated mitral stenosis. In multivalvular disease, pressures and resistance were frequently very high.

Physiologically significant tricuspid stenosis may be present with few diagnostic clues aside from a characteristic murmur. The classic signs and symptoms are most often associated with long-standing multivalvular disease.

The Angiocardiographic Diagnosis of Left Atrial Thrombosis

By *Jacob Zatuchni and Louis A. Soloff.* Department of Medicine, Temple University Medical School and Hospital, and Episcopal Hospital, Philadelphia.

This is the first report of visualization by angiocardiography of thrombi in the left atrium. Five instances were found in an angiocardiographic study of 57 consecutive individuals with rheumatic mitral stenosis. Of the 5, 2 were verified at operation and 1, with a ball-valve thrombus, was confirmed at necropsy. One did not have surgery because of age, coronary artery disease and angiocardiographic findings. The remaining 1 had no preoperative angiocardiogram. A thrombus found but not removed at surgery was demonstrated later by angiocardiography.

We use the biplane stereoscopic angiocardiographic apparatus of Chamberlain. Exposures of 0.1-sec. duration are made simultaneously in the posteroanterior and left lateral projections every 0.7 sec. for at least 21 seconds beginning with the onset of injection of 50 ml. 70% Urokon into an antecubital vein. A carotid sphygmogram allows for correlation of findings with phase of cardiac cycle. Stereoscopy is helpful in excluding change in opacity produced by extracardiac structures.

Opacification of the left atrium in mitral stenosis is intense, homogeneous and usually persists for longer than normal. Its borders are smooth, continuous and sharply defined. With mural thrombi, a filling defect is seen arising from an irregularly marginated posterior wall of the left atrium. With a ball-valve thrombus, a filling defect is seen unattached to the left atrial wall, and small compared to a myxoma. The left lateral projection is best for visualizing these defects.

The Problem of "Cerebral Embolization."

By *Albert W. Cook and E. Jefferson Browder.* Department of Neurosurgery, State University of New York, College of Medicine at New York City, Kings County Hospital, Brooklyn.

In the past, the sudden appearance of focal neurologic disturbances related to a cerebral hemisphere in the presence of a cardiac abnormality such as auricular fibrillation has prompted the designation "cerebral embolization" as the cause of the brain disorder. Little consideration has been directed to the vessel implicated in these processes and, in fact, pathologists rarely demonstrate the vascular trunk in the brain in which an embolus has lodged. Our data document the existence and importance of spontaneous lodgement of emboli in the carotid vessels in the neck. Although this is known to occur immediately following surgery on the heart, the spontaneous occurrence of emboli in these areas has not been emphasized.

The present study is of 4 patients, all of whom had rheumatic heart disease. In 3, auricular fibrillation was present at the time of onset of hemiplegia. In each instance the onset of a neurologic abnormality was precipitous and manifested by dysfunction of the left cerebral hemisphere. Percutaneous carotid arteriography verified carotid occlusion in each instance. In 3 patients the embolus was removed surgically. In the other, postmortem examination established the cervical position of the clot in the carotid system as well as the cerebral changes incident to embolic occlusion of the internal carotid artery.

Treatment thus far in situations of this character has been ineffective; however, an awareness of this pathoanatomic entity should prompt more intense consideration of the entire problem of so-called "cerebral embolization."

The Relation of Pulmonary Artery Size as Measured on the Angiocardiogram to Other Hemodynamic Phenomena

By *Fernando M. Martires, John J. Kelly, Jr. and Harold A. Lyons*

A study has been made of the relation of the size of the pulmonary artery as determined by angiocardiography to pulmonary artery pressures as measured by cardiac catheterization. Further evaluation of the relation between the size of the pulmonary artery and the intensity and timing of the first and second heart sounds has been made. The presence of a pulmonary artery systolic click, as related to the size of the pulmonary artery as measured, was also studied, as well as the correlation of the presence of systolic and diastolic murmurs as related to pulmonary artery measurements.

Studies on Mixing Volumes in the Central Circulation of Man and Dog

By *Hadley L. Conn, Jr. and Donald F. Heiman.* Robinette Foundation, University of Pennsylvania Medical School and Hospital of the University of Pennsylvania, Philadelphia.

Circulatory indicator-dilution curves as ordinarily determined have an exponential decline in slope. Model system studies by Newman have indicated that the value of this exponential will be a function of the largest mixing volume, normally pulmonary, providing the analogy between model and man is correct. Therefore, indicator injections at various sites proximal to the pulmonary vasculature should give identical dilution curve slopes, and injections beyond, much steeper slopes. These deductions were tested in normal dogs and in 12 patients, normal or with organic heart disease, but without evidence of "left-sided failure." Multiple

consecutive radiopotassium injections were made into various parts of the "right" and "left" circulations. Dilution curves were obtained from femoral arterial sampling.

In dogs and in 9 of 12 patients "right-sided" injections, regardless of injection site, gave nearly identical exponential slopes for each subject, while "left-sided" injections gave much different, steeper slopes. Specifically, calculated pulmonary mixing volumes remained constant within ±10% with volume ranges of 375–980 ml. in humans and 150–250 ml. in dogs. The indicated volume were not always large enough to represent the entire pulmonary volume, but certainly represented more than capillary volume, and apparently more than total pulmonary arterial and capillary volume. In 1 patient with tricuspid insufficiency the results indicated the transformation of right atrium and ventricle into a common mixing chamber with a volume considerably greater than the pulmonary mixing volume; and that this "new" chamber regulated the decline slope. Similarly, in 2 patients with mitral insufficiency the left heart volume was so large that it regulated the slope.

Conclusions from these results are: (1) the exponential dilution-curve slope, as predicted from model analysis, is a function of the largest existing central mixing volume; (2) this slope-governing volume is usually the pulmonary, but may be an extrapulmonary (cardiac) mixing volume under certain abnormal conditions.

The Clinical Recognition of Tricuspid Stenosis

By *John J. Kelly, Jr., Harold A. Lyons and Herbert N. Hultgren.* York University College of Medicine, New York City.

Tricuspid stenosis is a rarely recognized lesion, especially when associated with sinus rhythm. Because of the difficulty of making this diagnosis from a clinical examination, a report of our experience with this lesion may be of interest.

A history of decreasing orthopnea in the face of increased venous congestion is striking. Two patients with tricuspid stenosis, as the only significant valvular lesion, could sleep only in the prone position. When sinus rhythm is present, presystolic pulsation of the liver and the cervical veins is usually apparent. With auricular fibrillation, there is usually a systolic pulsation in the cervical veins suggestive of tricuspid insufficiency, but the veins do not collapse during diastole, as is usually the case in this latter condition. Very commonly, a sharp brief wave interrupts the giant A-wave of the jugular pulse. Phonocardiograms have demonstrated that this sharp wave is associated with a low pitched sound. Usually the presystolic murmur of tricuspid stenosis follows this sound. Along the lower edge of the sternum, the presystolic murmur of tricuspid stenosis can usually be heard. It is commonly accentuated by inspiration and diminished during expiration, unlike the murmur of mitral stenosis.

The vigorous contraction of the right atrium pushes the heart leftward, headward and posteriorly. This motion is reflected in leftward thrust of the heart as recorded by the apex beat, and in a large presystolic wave in the ballistocardiogram. Such traces are rare in mitral stenosis.

With the elevated pressure of right heart failure there is usually a large protodiastolic wave in the ballistocardiogram. This large protodiastolic wave is absent in tricuspid stenosis.

Hemodynamic data were also obtained by cardiac catheterization and angiocardiographic observations.

The Effect of Cigaret Smoking on Coronary Flow and Myocardial Metabolism in Man

By *L. M. Bargeron, F. Gonlubol, D. Ehmke and A. Calix.* Birmingham

The coronary blood flow, coronary resistance and myocardial usage of carbohydrate and noncarbohydrate material were measured in 10 patients before and during smoking a cigaret. Samples of blood were simultaneously drawn from a catheter introduced into the coronary sinus and from the femoral artery. Coronary blood flow was measured with the nitrous oxide method, cardiac output with the Fick principle. A cigaret was then smoked and the procedure repeated during or immediately following smoking. The tests were performed on smokers and nonsmokers. Smoking resulted in a consistent average rise in coronary blood flow (19%) and a consistent decrease in coronary resistance (27%). The myocardial oxygen usage rose 27%, and myocardial usages of glucose, pyruvate and lactate fell 15%, 18% and 11% respectively. Myocardial usage of ketones rose 36%. These data support the findings recorded in the literature that small doses of nicotine increase coronary artery blood flow and decrease coronary resistance. They also suggest that the ballistocardiographic and electrocardiographic effects of smoking occasionally seen in normal individuals may not be the result of myocardial ischemia.

Anaerobic Metabolism of the Myocardium and Other Organs during Exercise and Hypoxia

By *William E. Huckabee.* Massachusetts Memorial Hospital, Boston

Senile heart failure often cannot be attributed to "arteriosclerotic heart disease," but may be a derangement of myocardial metabolism unrelated to coronary narrowing. To assess this possibility, metabolic studies of myocardium supplied by vessels devoid of atherosclerosis were carried out and re-

vealed distinct alterations during mild exercise and hypoxia.

Coronary A-V differences for pyruvate, lactate and oxygen were measured at frequent intervals in normal dogs, during periods of rest and exercise, and during 15 and 10% oxygen breathing. Similar A-V differences were measured for limbs, liver and brain. Coronary blood flow increased 155 to 257% with exercise, 25% with 15% oxygen and 99% with 10% oxygen breathing; $(A\text{-}V)_{O_2}$ increased 12% with exercise and decreased 20% with hypoxia. Pyruvate and lactate A-V differences varied widely, without apparent pattern for all organs; they remained negative for the heart.

Anaerobic metabolic rates were calculated from the pyruvate and lactate exchanges with tissue. While crude A-V differences have no interpretable meaning, the curves of relative anaerobiosis of the myocardium rose progressively to high levels during exercise (10% ± 2% of total energy utilization) and during 10% oxygen (9.5% ± 2%), recovering afterward to control values. For the rest of the body this figure never exceeded 4%. Myocardial metabolism was entirely aerobic at rest during 21% and 15% oxygen breathing. Occasionally, rapid or transient changes occurred in anaerobic metabolism, again suggesting inadequate oxygen delivery not reflected in measured coronary blood flow.

It is concluded that metabolically inadequate coronary oxygen supply may be present during increased blood flow, whether or not cardiac work increases. Deleterious changes in metabolism of myocardium supplied by nonsclerotic vessels may be observed during mild stresses resembling ordinary activity, but these are the changes of increased anaerobic metabolism, indicating cellular hypoxia. Resulting damage to myocardial contractility would not be correlated solely with arteriosclerosis.

Serum Glutamic Oxalacetic Transaminase (SGO-T) Variations following Experimental and Clinical Coronary Insufficiency and Pericarditis

By *Irwin Nydick, Paul Ruegsegger, Felix Wroblewski and John S. LaDue.* Medical Service of Memorial Center for Cancer and Allied Diseases and the Sloan-Kettering Division, Cornell University Medical College, New York City.

The serum glutamic oxalacetic transaminase (SGO-T) activity increases significantly following experimental and clinical acute myocardial infarction and the height and duration of SGO-T elevation appears to be roughly proportional to the amount of heart muscle cell damage. Both clinical and experimental coronary insufficiency and pericarditis, however, fail to be associated with increased SGO-T activity unless accompanied by myocardial necrosis.

The SGO-T activity was followed in experimental coronary insufficiency. A thick braided silk ligature was placed beneath a major coronary vessel of a mongrel dog, the chest closed, and the ends of the ties brought to the chest wall and buried subcutaneously. Ten to 14 days later traction was applied to the tie, temporarily occluding the coronary vessel and tendering the myocardium ischemic. Occlusion was maintained for ½ to 7½ minutes. Striking abnormalities of the T waves and ST segments were noted on the electrocardiogram, within seconds after occlusion, which reverted to normal within 1 to 150 minutes after restoration of the patency of the vessel. No Q waves were produced.

The SGO-T remained within normal limits (15 to 45 U) in 9 of 10 dogs. A minimal transient rise was noted in the other animal. No evidence of myocardial necrosis was found at autopsy in any of these animals. Homogenates of normal myocardium and the temporarily ischemic myocardium of the same animal were equal in transaminase activity.

Fifty patients with status anginosus or severe coronary insufficiency were studied. Marked electrocardiographic abnormalities of the T waves and ST segments were present in all patients. The SGO-T was elevated in only 16 patients. These elevations showed no consistent relationship to the temperature, WBC or ESR, or the presence of congestive heart failure or mild shock.

Plastic catheters were sutured into the pericardial cavity of dogs, and pericarditis produced by the injection of talcum powder 2 weeks later. No rise in SGO-T occurred unless significant subepicardial myocardial necrosis was produced.

The SGO-T activity during the course of acute pericarditis of varied etiology remained within normal limits in 9 of 11 patients. Minor elevations occurred in 2 patients.

Experimental coronary insufficiency and pericarditis are not associated with any significant increase in SGO-T activity unless there is concomitant myocardial necrosis.

This suggests that when the SGO-T activity rises in man, during or following coronary insufficiency or pericarditis, myocardial damage has occurred.

Alterations in Serum Glutamic Oxalacetic Transaminase (SGO-T), Serum Glutamic Pyruvic Transaminase (SGP-T) and Lactic Dehydrogenase (LD) following Experimental Myocardial Infarction

By *Paul Ruegsegger, Irwin Nydick, Felix Wroblewski and John S. LaDue.* Medical Service of Memorial Center for Cancer and Allied Diseases and the Sloan-Kettering Division, Cornell University Medical College, New York City.

The serum glutamic oxalacetic transaminase (SGO-T) increases significantly following experimental myocardial infarction, and such elevations can be explained in part by the fact that SGO-T

is present in high concentration in the myocardium. The concentration of serum glutamic pyruvic transaminase (SGP-T) in dog heart is $\frac{1}{10}$th that of SGO-T. The concentration of lactic dehydrogenase (LD) in heart muscle is slightly greater than that of SGO-T, and all 3 enzymes are highly concentrated in liver tissue

Acute transmural infarction was produced in 10 dogs by tying of a ligature placed about the coronary artery 10 days previously, thus escaping the effect of anesthesia and operative trauma upon the activity of SGO-T, SGP-T and LD.

The activity of SGO-T following acute myocardial infarction was greater and remained elevated longer than LD activity. SGP-T activity was relatively unchanged. The concentration of the 3 enzymes in homogenates of infarcted and normal heart muscle were compared and contrasted with their relative serum activity. By use of these 3 enzyme systems it has been possible to differentiate heart and liver cell damage, since SGP-T rises precipitously following liver cell damage and insignificantly after myocardial necrosis. LD activity increases after myocardial necrosis, but is relatively unaltered following liver cell damage. SGO-T activity rises after both heart and liver cell injury. The concept of biochemical biopsy of tissues deserves further study.

The Mechanism and Significance of Alterations in Serum Glutamic Oxalacetic and Serum Glutamic Pyruvic Transaminase in Liver and Heart Disease

By *F. Wroblewski, C. Friend, I. Nydick, P. Ruegsegger and J. S. LaDue.* Memorial Center for Cancer and Allied Diseases, New York City.

Glutamic oxalacetic (GOT) and glutamic pyruvic (GPT) transaminase have been found to be widely distributed in animal and human tissues. GOT is particularly concentrated in cardiac muscle while GPT has its greatest concentration in liver tissue. These enzymes can be readily differentiated.

The serum activity of the enzymes was studied following the production of acute myocardial infarction in dogs and after the infection of mice with hepatitis virus. Similarly, the serum enzyme studies were made during the course of human transmural myocardial infarction and acute hepatitis.

Experimental and clinical myocardial infarctions are associated with a 2 to 20 times increase in serum GOT during the first 48 hours following cardiac necrosis, while no significant increase in GPT is simultaneously noted. Acute hepatocellular injury results in a rise of from 2 to 1000 times in serum GOT and GPT, the latter being greater than the former.

The mechanism for the increase in serum GOT associated with acute cardiac muscle injury appears to be primarily one of escape of GOT from necrotic cells, while the mechanism for increase of the serum enzymes during acute hepatocellular injury involves, in addition, a metabolic and/or excretory aberration.

Serum Glutamic Oxalacetic Transaminase in Tissue Ischemia

By *Lionel A. Rudolph, Robert E. Dutton, Jr., Robert Lindeman and Richard H. Lyons.* Department of Medicine, State University, New York College of Medicine, Syracuse.

Enzyme concentration in the venous drainage from organs subjected to intense but temporary ischemia by occlusion of major arterial vessels was studied. Myocardial venous blood in the ischemia studies was obtained through a catheter inserted through the external jugular vein into the coronary sinus of animals previously prepared with ligatures placed around coronary arteries. Multiple studies of the venous blood from kidney, spleen, intestine and heart for the first 12 hours following ischemia revealed no significant increase in enzyme concentration. Similar studies of venous blood from these organs subjected to infarction revealed a significant increase in enzyme concentration in from 3 to 6 hours following occlusion of the arterial blood supply.

Serum Glutamic Oxaloacetic Transaminase in Trauma

By *H. E. Ticktin, B. H. Ostrow and J. M. Evans.* George Washington Medical Division, the District of Columbia General Hospital and the George Washington University Hospital, The George Washington School of Medicine, Washington, D. C.

The enzyme, glutamic oxalacetic transaminase (GOT) is widely distributed in body tissues. Its concentration in skeletal muscle is second only to that in the myocardium. Since acute myocardial infarction and hepatocellular damage are associated with increased serum GOT, studies were undertaken to evaluate this enzyme in patients with trauma. GOT was studied within 24 hours of injury, and serially for at least 5 days in 12 patients. Acute myocardial infarction and active hepatocellular damage were excluded. GOT was determined by the method of Karmen, Wroblewski and LaDue with a normal range of 5 to 33 U/ml.

Of the 2 patients with burns, the one with second and third degree burns, involving 65% of the body surface, had the highest GOT level observed in the study, 322 U/ml. The second patient had first and second degree burns involving 25% of the body surface and a normal GOT.

The remaining patients, all with fractures, were classified as moderate or severe on the basis of the

extent of muscle injury. There were 4 severe injuries, all showing increased GOT, with an average of 80 U/ml. Of the 6 cases with moderate injury and a minimum of muscle damage, only 3 had increased GOT levels, averaging 30 U/ml.

These observations indicate that acute injury to peripheral tissues liberates GOT into the serum. Levels of the magnitude recorded in acute myocardial infarction or hepatocellular damage are seen only with extensive muscle damage or wide-spread burns.

The Diagnosis of Incomplete Left Bundle Branch Block

By *Sami Said, Henry M. McLaughlin, Mahdi Murtadha and J. Marion Bryant.* Fourth Medical (N.Y.U.) Division, Bellevue Hospital, and the Department of Medicine, New York University Post-Graduate Medical School, New York City. (Aided by a grant from the Lillia Babbitt Hyde Foundation.)

Incomplete left bundle branch block is a well-recognized, though poorly defined, electrocardiographic entity. Its recognition is important, primarily because it may mask or simulate the diagnosis of myocardial infarction and, secondarily, because its presence is usually associated with heart disease. However, investigators are not in agreement concerning its diagnostic criteria. Wilson indicated that the absence of Q waves in V_5 and V_6 may suggest the diagnosis. However, a large percentage of subjects with no Q waves in V_5 and V_6 show Q waves in V_7 and V_8.

Sodi-Pollares et al., as the result of studies in animals and man in which potentials were recorded from the right and left ventricular cavities, have proposed that slurring of the upstroke of the R wave in left ventricular leads, in the absence or presence of Q waves, indicates the presence of incomplete left bundle branch block.

Small Q waves are present in right precordial leads (V_1 and V_2) in some cases of incomplete left bundle branch block due to the reversal of direction of *initial* trans-septal activation. However, such Q waves have also been found in normal subjects in leads from slightly higher sites.

Simultaneous tracings (Sanborn twin-beam instrument) were taken from the right and left precordium in patients with incomplete left bundle branch block, confirmed by right ventricular intracavity leads and by the presence of initial positive deflections in esophageal leads from atrial levels. "Q waves" from left precordial sites were preceded by isoelectric periods or indistinct initial deflections. Therefore, in these cases there were no true Q waves in V_5 and V_7 consistent with normal initial negativity of the left ventricular cavity. This is compatible with the presence of abnormal left bundle branch conduction.

While these findings suggest that the diagnostic criteria of incomplete left bundle branch block are still indefinite, they indicate that simultaneous recordings of leads from the right and left precordium are helpful in establishing the diagnosis.

Effect of Calcium on the Ballistocardiogram

By *Harold Kallman and Richard Gubner.* Department of Medicine, Kings County Hospital, Brooklyn; the Equitable Life Assurance Society of the United States.

The effect of calcium on cardiac contraction was investigated by observing ballistocardiographic changes following administration of 1 Gm. calcium gluconate intravenously in 10 nondigitalized patients with heart disease whose control ballistocardiograms were abnormal. Velocity ballistocardiograms were recorded in suspended expiration (which best reflects left ventricular contraction) before and at minute intervals following calcium administration. In all instances significant changes appeared within 1 to 2 minutes, which persisted during a 15-minute period of observation. I and J waves increased in amplitude, and the complexes assumed a more normal and regular appearance. An increased vigor of cardiac contraction and augmented stroke output was reflected also by widening of the pulse pressure, averaging 21 mm. Hg. The heart rate decreased 8.6 beats/min.

In 4 patients, observations were made also, on different days, of the effects of intravenous administration of acetyl strophanthidin (3 cat U) and nicotinic acid (300 mg.) Acetyl strophanthidin caused a minimal increase in pulse pressure, averaging 3 mm. Hg, and a decrease in heart rate averaging 4.25 beats/min. These effects first appeared 7 to 10 minutes following injection. The ballistocardiographic changes were far less conspicuous than those produced by calcium. Nicotinic acid was given to evaluate the possible role of peripheral vasodilatation in accounting for the ballistocardiographic changes produced by calcium. It caused a negligible drop in pulse pressure, a slight rise in pulse rate and a fall in diastolic pressure averaging 14 mm. Hg. The only ballistocardiographic effect was the appearance of a prominent diastolic L wave.

These observations indicate that intravenous calcium causes an almost immediate augmentation in cardiac force, exceeding that produced by acetyl strophanthidin, and provide a rationale for the prompt favorable effect we have noted following intravenous calcium administration in several patients with acute pulmonary edema.

Influence of Pronestyl on Myocardial Ionic Exchange and Cardiac Arrhythmias Induced by Acetyl Strophanthidin

By *Timothy J. Regan, Frederick N. Talmers, Raymond C. Christensen, Takashi Wada and Harper*

K. Hellems. Department of Medicine, Wayne University College of Medicine, Detroit.

The effective cardiac antiarrhythmic agents have shown varied pharmacologic properties, none of which appear essential to their activity. Since electrolytes bear an important relation to electric properties of tissue, a study of myocardial Na and K transfers was undertaken in 1 group of dogs given acetyl strophanthidin (.05 mg./Kg.) and a 2nd group pretreated with the antiarrhythmic, Pronestyl, before receiving the digitalis analog.

The A-V difference of these ions was used as a measure of their myocardial exchange, simultaneous samples being taken from the femoral artery and catheterized coronary sinus in a control period and at frequent intervals after each drug.

In the group of 8 animals which received strophanthidin alone, the control A-V difference values for potassium were not significant, 0.10 ± .14 mEq./L. (K_A 4.15, K_{cs} 4.05 mEq./L.). After the infusion of acetyl strophanthidin, there was abrupt loss of K, reaching a maximum negative A-V difference of 0.86 ± .44 mEq./L. (K_A 4.87 mEq./L., K_{cs} 5.73 mEq./L.), $p < .001$ at 6 min. Control A-V difference for sodium was −3 ± 4 mEq./L. (Na_A 151 mEq./L., Na_{cs} 154 mEq./L.). Concurrent with the K loss there occurred Na uptake with a maximum A-V difference of +6 ± 4 mEq./L. (Na_A 153 mEq./L., Na_{cs} 147 mEq./L.). Both ionic changes gradually returned to control by 30 min.

In the group of 7 animals pretreated with Pronestyl 5 minutes before receiving strophanthidin, the control potassium A-V difference was negligible, −.03 ± .34 mEq./L. (K_A 3.92 mEq./L., K_{cs} 3.95 mEq./L.). Pronestyl did not significantly alter this relationship. After strophanthidin, there was rapid egress of cellular K with a maximum negative A-V difference of 0.71 ± .23 mEq./L. (K_A 4.47 mEq./L., K_{cs} 5.18 mEq./L.), $p < .01$. Control sodium A-V difference was −1.0 ± 2.7 mEq./L. (Na_A 154 mEq./L., Na_{cs} 155 mEq./L.). Pronestyl did not change these sodium values. After strophanthidin, the maximum A-V difference change was −4 ± 4.7 mEq./L. (Na_A 150 mEq./L., Na_{cs} 154 mEq./L.).

The Pronestyl pretreated group had no arrhythmias, while there was a 50% incidence in the group receiving strophanthidin alone. The presence of significant myocardial Na uptake in the latter group, with blockade of this response in the Pronestyl group, suggests a possible relationship of this ion to digitalis-induced arrhythmias.

The Hemodynamic Effects of Quinidine in Dogs

By *George G. Rowe, Dean A. Emanuel, George M. Maxwell, John F. Brown, César C. Alzamora, Benjamin Schuster, Q. R. Murphy and Charles W. Crumpton.* Department of Medicine, University of Wisconsin School of Medicine, Madison.

Cardiac output and coronary blood flow were determined by means of the Fick principle and N_2O method, respectively, in 13 dogs. Studies were made before and an average of 24 minutes after rapid intravenous injection of 15 mg./Kg. of quinidine gluconate in 9 dogs, and after intravenous infusion of the same dose over a 20-minute period in 4 dogs. The hemodynamic effects of the drug were essentially the same by these 2 methods of administration, so the data are grouped and considered together. Tachycardia and hypotension occurred immediately after the drug. At the time of the second study, the cardiac rate remained significantly elevated (+98%, $p < 0.001$) but the mean arterial blood pressure had risen again, averaging only 7% below control determinations ($p < 0.1$). The pulmonary arterial mean pressure was 29% lower ($p < 0.001$) at the second study. Although O_2 consumption increased (12%, $p < 0.001$), the arterial-mixed venous oxygen difference increased also (21%, $p < 0.001$) and cardiac output remained unchanged ($p > 0.9$). Stroke volume was reduced by 50% ($p < 0.001$). Left ventricular work did not change significantly (−9%, $p < 0.1$), nor did systemic vascular resistance (−1%).

Coronary hemodynamic changes were striking. In spite of the 46% increase in coronary blood flow ($p < 0.001$), there was a 40% decrease in coronary sinus O_2 ($p < 0.001$) and a 19% increase in myocardial oxygen extraction ($p < 0.001$). Left ventricular myocardial oxygen utilization increased by 77% ($p < 0.001$). Coronary vascular resistance fell 44% ($p < 0.001$). Although the coronary blood flow/Kg. M. of left ventricular work increased 63% ($p < 0.001$), the flow per beat decreased 27% ($p < 0.01$), and myocardial efficiency, measured as Kg. M. of left ventricular work/cc. of oxygen utilized, fell markedly (45%, $p < 0.001$). This adverse effect on the myocardial efficiency may well be regarded as a quantitative measurement of the cardiac toxicity of quinidine.

A Study of Hemodynamics during Atrial Flutter and Spontaneous Reversion to Normal Sinus Rhythm

By *Peter Mahrer, Thomas Killip, III and Daniel S. Lukas.* Department of Medicine and Cardio-Pulmonary Laboratory, New York Hospital-Cornell Medical Center, New York. (Aided by a grant from the National Heart Institute.)

The effects of atrial flutter on hemodynamics are difficult to evaluate because factors other than a shift in pacemaker may influence cardiovascular function in the interval between normal sinus rhythm (NSR) and flutter.

An ideal experimental situation was encountered when (during the course of a cardiac catheterization of a 31-year-old female, 29 months postmitral valvuloplasty) atrial flutter at a ventricular rate of 100/min. developed, persisted for an hour and then

spontaneously reverted to NSR at 100/min. An evaluation of resting hemodynamics during both rhythms was performed. The cardiac output during flutter was 3.30 L./min./M.² and during NSR was 2.84 L./min./M.² The decrease was due to a 22 cc./min./M.² fall in oxygen consumption, and not to an intrinsic alteration in cardiac function, since the A-V_{O_2} difference remained at 4.6 vol.%. The respiratory quotient was identical during both periods. "PC" pressures were 21 and 20 mm. Hg; pulmonary arterial, 47/25 and 48/27 with means of 38 and 39; right ventricular pressures, 47/2 and 48/3 mm. Hg during flutter and NSR respectively. Conclusive evidence of mitral and tricuspid insufficiency was observed during flutter in the "PC" and right atrial pressure curves respectively, but disappeared during NSR.

Under the circumstances of this study, in which the influence of drugs, bed rest and change in ventricular rate could be excluded, atrial flutter had no effect on resting cardiac output and pressures in the right ventricle and pulmonary vascular bed, but definitely impaired the mechanism of closure of the atrioventricular valves.

Transesophageal Ventricular Defibrillation

By *Gerald H. Whipple and George B. Penton.* Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School, Boston. (Aided by a grant from the Charles E. Merrill Cardiac Research Fund.)

Previous attempts at electric ventricular defibrillation of the larger mammals through the unopened thorax have usually been unsuccessful or impractical. The large amount of current required has been a recurring stumbling block. Consequently, the possibility of reducing the amount of current necessary by placing one of the defibrillating electrodes in the esophagus was investigated.

Ventricular fibrillation was induced with alternating current in large mongrel dogs under sodium pentobarbital anesthesia. For defibrillation, a flexible esophageal electrode of braided copper, 15 cm. long and 9 mm. in diameter, was used in conjunction with a precordial electrode of malleable sheet lead, 30 cm. in diameter. The average body resistance under these circumstances was about 100 ohms. Sinusoidal 60-cycle alternating current shocks lasting 0.1 second were applied to these electrodes.

Survival was the rule, if the shocks were given within one minute of the onset of ventricular fibrillation; ventricular defibrillation uniformly resulted if the shocks were given within 5 minutes of the onset. Voltages from 120 to 400 volts were used; the larger values were needed only if several minutes had been allowed to elapse before the defibrillatory shocks were administered. In the latter case, the dogs did not survive despite defibrillation owing to the hypodynamic character of the postfibrillatory beats.

It is concluded that survival in dogs after uniformly successful ventricular defibrillation through the unopened chest can be achieved with ordinary current sources under the limiting conditions described.

Coenzyme A Activity in Congestive Heart Failure

By *Michael G. Wohl, Charles R. Shuman, Richard Turner and Martin Brody.* Nutrition Project, Philadelphia General Hospital and Temple University Hospital, Philadelphia.

Patients with congestive heart failure due to hypertensive, arteriosclerotic and valvular heart diseases were subjects of this study in which para-aminobenzoic acid (PABA) was given in order to to determine the rate of acetylation of this substance as a measure of coenzyme A activity. Previous observations have disclosed that subclinical thiamine cocarboxylase deficits are consistently found in heart muscle of congestive failure patients. It appeared desirable to measure the level of activity of other components of the vitamin B complex group, such as pantothenic acid—the essential factor in the formation of coenzyme A. Initially, PABA was administered by mouth in doses of 500 mg. to 17 patients with chronic heart failure and to 8 control, noncardiac patients residing in the same wards. The test substance (PABA) was then given intravenously, 500 mg. to 8 additional cardiac failure patients and to 8 control patients by the same route for comparison. Following the administration of the drug by either oral or intravenous routes, urine was collected for a 12-hour period. The free and total PABA excretions for 12 hours were determined by the method of Bratton and Marshall. The percentage of acetylated PABA used to reflect coenzyme A activity was calculated from the differences between free and total PABA.

$$\left(\text{acetylated PABA} = \frac{\text{total} - \text{free PABA}}{\text{total PABA}} \times 100\right)$$

The results of this study indicated that there were statistically insignificant differences in the acetylating capacity of PABA between the control and cardiac failure groups. The mean values for cardiac patients were 93.24% for the oral route, and 83.1% for the intravenous route. The mean values for the control patients were 92.6% and 66.7% respectively. It would appear that the acetylation process, and presumably coenzyme A activity, is not impaired in patients with heart failure. This finding may reflect the wide availability of pantothenic acid necessary to maintain coenzyme A activity in cardiac failure.

Alterations in Exchangeable Potassium Content during the Therapy of Congestive Failure

By *Jerry K. Aikawa and Reginald H. Fitz.* Department of Medicine, University of Colorado School of Medicine, Denver. (Aided by a grant from the American Heart Association and the U. S. Atomic Energy Commission.)

The in vivo isotope dilution technic was used to study exchangeable potassium content (Ke) during therapy of congestive failure. Serial determinations were made in 11 hospitalized patients (8 men and 3 women). Ke changes were correlated with clinical response and changes in serum electrolyte concentrations and body weight.

Nine of 11 initial Ke and Ke/wt. values were below the normal range. Subjects were divided into 2 groups on the basis of clinical course.

Group 1: Seven patients had a satisfactory clinical course with diuresis, weight loss and amelioration of symptoms. In 6, Ke increased as weight decreased. A mean weekly Ke increase of 262 mEq. (range, 90–879) from a mean initial value of 2033 mEq. (range, 1635–2655) occurred as weight decreased a mean of 3.2 Kg. (range, 1.4–4.4). Serum electrolyte concentrations showed no striking changes. The seventh showed a weekly Ke decrease of 228 mEq., and 2.8 Kg. in weight; serum sodium decreased 15 mEq./L.

Group 2: Clinical response was unsatisfactory in 4 patients. Two had protracted convalescence, the first with a pulmonary infarct between Ke determinations. Ke decreased by 555 and 108 mEq. as weight decreased 5.2 and 3.6 Kg. respectively. The third subject had progressive decrease in Ke and died in intractable failure with multiple pulmonary infarctions. In all 3, serum sodium decreased at least 3 mEq./L. as Ke decreased at least 300 mEq.; serum potassium values remained unchanged. The fourth patient gained weight; Ke and serum sodium rose.

Ke may be depleted during the development of congestive failure and replenished during therapy, even when body-weight is decreasing. Increase in the severity of failure, or a complication such as pulmonary infarction, may be accompanied by further decrease in Ke.

Hemodynamic Effects of Large-Dose Infusions of Norepinephrine during Pulmonary Arterial Constriction

By *N. O. Fowler, R. H. Franch and E. R. Duchesne.* Department of Medicine, Emory University and Cardiovascular Laboratory, Grady Memorial Hospital, Atlanta, Georgia.

Unpublished observations have shown that norepinephrine increases the cardiac output of the anesthetized dog. This study was undertaken to ascertain whether norepinephrine can increase cardiac output in the intact animal with increased cardiac work-load. The main pulmonary artery of 11 dogs was progressively constricted until right ventricular systolic pressure increased 50–200%, or until systemic arterial pressure fell (period 1). Norepinephrine, 3–6 μg./Kg./min. was then infused for 15–30 minutes (period 2). After a 15-minute recovery (period 3), a second infusion of norepinephrine was given (period 4). During the control period and periods 1–4, measurements were made of pulmonary arterial, right atrial and carotid arterial pressures, and of direct Fick cardiac output.

Control cardiac outputs were 118 ± 15 cc./Kg./min. With pulmonary constriction, cardiac outputs fell significantly, 69 ± 14 cc./Kg./min., $p < 0.05$. During the first norepinephrine infusion, cardiac outputs increased significantly, 124 ± 14 cc./Kg./min., $p < 0.01$. After discontinuance of norepinephrine, cardiac outputs fell significantly to 51 ± 7 cc./Kg./min., $p < 0.001$. During a second norepinephrine infusion, a significant increase in cardiac output to 118 ± 18 cc./Kg./min., $p < 0.01$, again occurred. During norepinephrine infusion, heart rate increased significantly, systemic arterial pressure rose significantly, and the heart decreased in size—more strikingly if previously dilated. Cardiac output and strength of contraction were less after norepinephrine infusion than before. Because of its dramatic effect, cardiac action during norepinephrine infusion will be demonstrated by a 5-minute color motion picture. It is concluded that norepinephrine in the presence of acute induced pulmonary arterial constriction produces the following effects: increase in cardiac output, increase in heart rate, and reduction in size of the acutely dilated right heart.

Incrimination of the Capillary Bed in the Pathogenesis of Acute Hypertension

By *Frank A. Finnerty, Jr. and Robert L. Guillaudeu.* Department of Medicine, Georgetown University School of Medicine, and the Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.

Many investigators have demonstrated that severe toxemia of pregnancy is associated with hemoconcentration and that clinical improvement is associated with gradual blood dilution. Observations in 4 patients with severe toxemia of pregnancy (2 patients with eclampsia) have shown a 25% increase in plasma volume and decrease in hematocrit immediately following reduction of arterial pressure. To determine the specificity of these changes for toxemia, and perhaps to throw light on the pathogenesis of a fluid shift, serial plasma volume determinations (T-1824) were performed before and immediately after acute reduction of arterial pressure in 3 groups of patients. Serial cardiac output determinations were also performed in order that

the mean circulation time and central blood volume might be calculated.

Acute reduction of arterial pressure in 4 patients with moderately severe toxemia was accompanied by an 18 ± 28% increase in plasma volume. Acute reduction in arterial pressure in 7 nonpregnant patients with chronic hypertension and 2 normotensive patients was accompanied by no change in either plasma volume or hematocrit. In 6 patients with acute hypertension (2 malignant, 1 encephalopathy, 2 with recent flame-shaped hemorrhages in the fundi, 1 postpartum hypertension), a 33% reduction of arterial pressure was accompanied by a 26 ± 11.3% increase in plasma volume and decrease in hematocrit.

These changes seemed to be unrelated to either the drug given or secondary to a change in cardiac output, since Veratrum was used in 2 instances, hexamethonium in 2 and hydralazine in 3 instances, and the cardiac output was elevated in 3 and decreased in 3 instances.

It would seem from these data that: (1) hemoconcentration is not a specific finding for toxemia of pregnancy but is present in any *acute* hypertensive state, regardless of cause; and (2) acute reduction of arterial pressure under such circumstances is accompanied by hemodilution. Although the cause of this hemodilution remains unknown, it would seem that the capillary bed must be incriminated in some fashion to explain this shift in fluid. Studies are in progress to determine whether such acute reduction in arterial pressure is related to an increase in the oncotic pressure or a decrease in the capillary filtration pressure.

The Natural History of Hypertensive Retinopathy as Revealed by Serial Color Photographs

By *Albert A. Brust.* Department of Internal Medicine, Emory University School of Medicine and the Grady Memorial Hospital, Atlanta.

The eyeground manifestations of hypertension, though varied and diverse, are believed to supply valuable diagnostic and perhaps prognostic information. As part of a more general investigative study of hypertension, color photographs of the eyegrounds (Bausch and Lomb funduscopic camera) have been taken at frequent intervals, and an attempt made to correlate the changes with the clinical course of the disease. For comparison purposes the fundi of patients with diabetes, anemias, renal and collagen disease have also been studied. By this method, subtle as well as gross changes have been documented in serial fashion, so that the natural history and potential reversibility of hemorrhagic, exudative and edematous changes in many of the retinopathies can be more clearly defined.

Serial color photographs in selected patients demonstrate characteristic differences in the retinal hemorrhages associated with accelerated hypertension, diabetes, anemia and subarachnoid bleeding; the rapidity with which hemorrhages and exudates may appear and disappear without residual; and, finally, the progression and regression of hypertensive retinopathy with and without depressor drug therapy.

This photographic technic not only offers valuable clinical information, but appears to lend itself particularly well as a helpful tool for the investigation of vascular disease.

Studies on Mechanism of Tolerance to Ganglion-Blocking Drugs

By *G. G. Langford and J. Harbour.* Departments of Medicine, University and V. A. Hospital, Jackson, Mississippi.

During the first month of therapy of hypertension with ganglion-blocking drugs the dose required to produce a given lowering of blood pressure may increase to 10-fold of that initially required. This tolerance has been attributed to increased activity of a "nephrogenic" factor. To study another possibility—that of decreasing effect of the drug as an autonomic blocking agent—an independent measure of autonomic activity was desired. The effect upon accommodation (near-point) was chosen. Eleven patients with severe hypertension have been followed from 2 weeks to 3 months. Supine and standing blood pressures and near-point of the eye have been determined repeatedly, prior to and during ganglionic blockade therapy. In 10 out of 11 of the patients there was concomitant variation of near-point and blood pressure, with the near-point receding from the eye at the same time that the pressure is lowered. Then, with increasing tolerance, both near-point and blood pressure tend to return to control values. If dosage is increased adequately to maintain blood pressure lowering, there will be no further change in near-point.

Because of the parallelism of these 2 independently determined effects, both of which are mediated via the autonomic nervous system, we feel that the common factor in tolerance is decreasing ability of the drug to produce ganglionic blockade. This drug tolerance, rather than increase of a "nephrogenic" component, is considered the primary cause of diminishing hypotensive response on a fixed dose of a ganglion-blocking drug.

The Effect of Intravenously Administered Ecolid (SU-3088) on Renal Function in Hypertensive Patients

By *Charles M. Ebner and Yoshikazu Morita.* Department of Medicine, Wayne University College of Medicine, and City of Detroit Receiving Hospital, Detroit.

The effect of intravenously administered Ecolid (SU-3088), a ganglionic blocking agent, on

renal plasma flow (RPF) and glomerular filtration rate (GFR) was studied in 5 hypertensive patients. The subjects were inclined at 30° from the horizontal during the study. After control measurements, 2.5 to 10 mg. of Ecolid were given intravenously. At 1 and 2 hours after the injection, repeat clearances were performed. In all patients the mean blood pressure fell. Except for the patient who received the 2.5 mg. dose, the drop was at least 49 mm. Hg, and persisted throughout the 2-hour period. RPF fell significantly in 3 patients in 1 hour, and was still low at 2 hours. In 1, a fall in RPF did not occur until the second hour, although a good hypotensive effect was obtained at the end of 1 hour. In another subject, there was no significant change in the RPF despite a good hypotensive effect. The range for control RPF in the 5 cases was 119 to 286 ml./min./1.73 M.², with a mean of 189 ml./min./1.73 M.² At the first hour, the changes in RPF were −57, −54, −29, +8 and +8 ml./min./1.73 M.²; at the second hour they were −47, −40, −29, −29, and +6 ml./min./1.73 M.² GFR fell in every case, and the filtration fraction fell toward or to normal. The change in GFR at the first hour ranged from −25 to −10 ml./min./1.73 M.²; at the second hour, from −28 to −11 ml./min./1.73 M.² The calculated total renal resistance fell in 4 patients, and did not change in the patient who had received the 2.5 mg. dose. It is concluded that Ecolid, given under the conditions above, usually produces a fall in the GFR, RPF and renal resistance, which persists for at least 2 hours.

The Serum Lipids in Hypertensive Patients Treated with Pentolinium

By *Harold H. Orvis, Irene G. Tamagna and John M. Evans.* Department of Medicine, the George Washington University School of Medicine, Washington, D. C.

Twelve patients with severe hypertension were treated with pentolinium for 1 year. At periodic intervals, fasting blood was analyzed for serum cholesterol and β lipoprotein (by paper electrophoresis). Ten patients had initial hypercholesterolemia greater than 250 mg.%. Of these 10, 8 sustained a drop in cholesterol averaging 81 mg.% at 4 months and 101 mg.% at 8 months. Six of the original patients exhibited a rise in β lipoprotein averaging 15.4.% at 4 to 6 months. Generally, the increase resulted from prolongation of the β lipoprotein curve in the region of greatest migration.

A 6-week placebo period was instituted in 6 of the 12 treated patients. Fasting sera were analyzed for total lipids, cholesterol, cholesterol esters and % β lipoprotein. In 3 of the 6 patients, total serum lipids increased during this period compared with preplacebo values, the increase averaging 162 mg.%. In 5 patients, cholesterol and cholesterol esters rose during placebo administration, averaging 46 and 34 mg.% respectively. In 4 patients β lipoprotein fell an average of 14.5% at the 6th week of the placebo administration. An oral fat tolerance test, performed while on pentolinium and in the 3rd week of the placebo, showed that the serum turbidity was higher at 3 hours after fat ingestion in the 3rd-week determination in all 6 patients.

In contrast to the above findings, in 1 patient exhibiting marked blood pressure response to reserpine, and 1 patient relieved of hypertension by surgery for coarctation of the aorta, there was no change in fasting serum lipid after treatment.

These data indicate that coincident with pentolinium therapy, a decline in fasting serum lipids and redistribution of lipoprotein may occur. This may be explained, at least in part, by altered lipid absorption as a consequence of pentolinium administration.

The Cardiovascular Evaluation in Man of a Pressor Amine, DL 2-(1,2,3,4-Tetrahydro-1-Naphthyl)-Imidazoline (Tetrahydrozoline), Showing Hypotensive Properties

By *Frank A. Finnerty, Jr., Robert L. Guillaudeu and Joachim H. Buchholz.* Department of Medicine, Georgetown University School of Medicine and the Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.

DL 2-(1,2,3,4-tetrahydro-1-naphthyl)imidazoline (tetrahydrozoline), a pressor amine closely related chemically and pharmacologically to naphazoline, has been shown to have definite hypotensive properties in man.

Six to 10 mg./day of tetrahydrozoline given in divided doses for an average of 9 weeks to 18 moderately severe hypertensive patients (Grade II and Grade III fundi) resulted in an average fall in arterial pressure of 37 mm. Hg systolic and 29 mm. Hg diastolic and an average decrease in pulse rate of 15 beats/min. When tetrahydrozoline was given intravenously to 33 patients in a dosage of 1.5 mg., there was an average reduction in systolic pressure of 41 mm. Hg and in diastolic pressure of 27 mm. Hg. A pressor response unaccompanied by any untoward side effects was noted during the first 5 minutes after injection in 6 patients. Although mild drowsiness was seen in 13 of 18 patients who received oral medication, and in 10 of 33 patients who received the drug intravenously, medication had to be discontinued in only 5 patients.

No significant fall in cardiac output (Hamilton dye dilution technic) was seen in 4 patients studied who received the drug orally, but a 30% reduction in cardiac output followed reduction of arterial pressure with intravenous tetrahydrozoline in the 2 patients studied. Renal blood flow and creatinine clearance decreased proportionately to the fall in cardiac output in the 4 cases studied. No significant

change was seen in the venous pressure. The bradycardia could be overcome by atropine.

Although slight blockade of the pressor response to noxious stimuli could be demonstrated, tetrahydrozoline neither consistently blocked nor potentiated the pressor response of epinephrine. These data, plus the frequent finding of postural hypotension, would suggest that tetrahydrozoline is a weak, centrally-acting sympatholytic drug with vagotonic properties.

Although the undesirable hypnotic effects will limit the usefulness of tetrahydrozoline, it is hoped that these preliminary studies will stimulate further investigations of other derivatives of 2-imidazoline in hopes of uncovering a clinically useful hypotensive agent.

Alkali Therapy for Postsympathectomy Postural Hypotension in the Presence of Mild Acidosis

By *F. J. Haddy, F. W. Wokalek and L. T. Minish, Jr.* the Norton Infirmary, Louisville, Ky.

A 52-year-old woman was hospitalized because of postural faintness and/or syncope of 5 weeks duration. The past history revealed the onset of hypertension with evidence of renal damage 7 years previously, followed in 3 years by a bilateral thoracolumbar sympathectomy. The recumbent blood pressure varied between 135–185 systolic and 80–100 diastolic. The maximum recorded blood pressure immediately on standing was 80/60. More than a minute in the upright position resulted in tachycardia, disappearance of pulse and blood pressure and faintness followed by syncope. Pertinent laboratory data included slight albuminuria, low fixed urinary specific gravity, blood NPN 66 mg.% and blood CO_2 combining power 23.4 mEq./L. Since a study by Burget and Visscher had indicated that epinephrine is more active on the vascular system in an alkalotic than acidotic animal, it was decided to test the effect of alkaline therapy on the postural blood pressure changes exhibited by this patient. Two hundred cc. of ⅙ M sodium lactate were administered intravenously over a 1-hour period. Immediately following therapy, the patient walked without symptoms, and blood pressure did not fall below 100/70. The patient remained asymptomatic for 60 hours, after which there was a recurrence of syncope and hypotension on standing (CO_2 22 mEq./L.). Twenty Gm. of sodium bicarbonate were administered orally over a 24-hour period. The patient was again asymptomatic with a minimal standing blood pressure of 110/78 (CO_2 26 mEq./L.). The sodium bicarbonate was discontinued. Eighteen hours later the signs and symptoms recurred in their entirety (CO_2 22 mEq./L.). Bicarbonate therapy was reinstituted. Twenty four hours later the patient walked asymptomatically with a minimum blood pressure of 100/70 (CO_2 27 mEq./L.).

Carotid Oscillograms in Arterial Disease

By *A. S. Dontas.* Department of Internal Medicine, University Hospital, Ann Arbor

Study of oscillograms of right and left common carotid artery was undertaken in 20 normals, 20 hypertensives in no failure and 8 diabetics of comparable age. Oscillograms were obtained by inflating to 50 mm. Hg a child-sized pressure cuff around the lower neck, while protecting the other half of the neck and its large vessels with a plastic cover. The cuff was connected to a Statham P23A gage, supplied with DC excitation and followed by 3 stages of amplification, the last one being AC, with time constant of 2 seconds. The amplifier output was fed into an oscilloscope along with an electrocardiographic lead.

Such oscillograms displayed the typical "central pressure pulse" features obtained in man and animal by arterial puncture. Their form was repeatable from day to day and was not altered by spontaneous or drug-induced blood pressure changes. Their ascending limb had a uniform angle in normals with the inflection point occurring at 62 to 95% of the total height of each curve; this ratio was the same in both carotids on the normals tested. Hypertensives and diabetics displayed both a significantly decreased ratio (inflection point occurring at 30 to 80% of the total pulse height) and widely differing ratios in the 2 sides, which might be explained as decreased carotid distensibility in both these groups. Pulse wave velocity, ascending and descending slopes, showed no consistent changes in any of these groups.

This simple, quantitative method gives reproducible results, and is a useful tool in the study of arterial disease.

Serum Lipoproteins in Peripheral Arteriosclerosis

By *Norman H. Azen, Lena L. Lewis and Victor G. deWolfe.* Department of Medicine and the Research Division, the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland. (Aided by a grant from the National Heart Institute.)

Serum lipoprotein concentrations ($-S_{1\text{-}21}$, Green, Lewis and Page modification of Gofman's procedure) were measured in 84 nondiabetic patients with peripheral or aortic atherosclerosis demonstrated by angiograms, concurrently with determinations of serum cholesterol. The method used determines high-density lipoproteins ($-S$ 1–10) and those of low density ($-S$, 70–400, 40–70, 25–40), correspondingly approximately to α and β lipoproteins.

The averages of the group indicate increases in concentrations of serum cholesterol and low-density lipoproteins with a decrease in high-density lipoprotein content. Definite increases in low-density

lipoprotein content were found in 21 (25%) and probable increases in 15 (18%), with normal values in 48 (57%). Incidences of increased serum low-density lipoprotein concentrations were nearly the same in patients with extensive as in those with segmental atherosclerosis.

In comparison with a normal population of the same age, these patients show an increased incidence of high concentrations of low-density lipoproteins, with concurrent increases in serum cholesterol and decreases in high-density lipoprotein concentrations. However, these abnormalities are demonstrable in less than half of the patients, and show no association with the extent of the arterial disease. The observations support the view that abnormalities of serum lipoprotein may participate in the pathogenesis of arteriosclerosis, but indicate also that other unrecognized factors are of equal or greater significance.

Comparative Vasoconstrictor Effects of Smoking Cigarets in Warm and Cool Environments and before and after Abstinence from Tobacco

By *John W. Eckstein, J. Edwin Wood and Robert W. Wilkins.* Evans Memorial, Massachusetts Memorial Hospitals, Boston.

Vasoconstrictor responses to smoking 2 cigarets were measured by venous occlusion plethysmography in the feet of normal habitual smokers. The measurements were made at warm (83°F.) and cool (68°F.) room temperatures and were repeated in the same subjects after abstinence from tobacco for 24 to 48 hours. The averages of all the measurements during the first 30 minutes after the start of smoking were compared percentally with the averages of all the control measurements.

In 23 of 26 experiments foot blood flow was reduced after smoking to 45 to 93% (average 79.3%) of the control values. The vasoconstrictor response in the foot usually began with the first inhalations of smoke, tended to remit even during the smoking, and passed off usually within 40 minutes in the warm room and 60 minutes in the cool room.

In 12 paired experiments the vasoconstrictor responses to smoking averaged the same in the warm and the cool rooms. Likewise, in 11 other paired experiments the vasoconstrictor responses to smoking averaged the same before and after abstinence from tobacco. In each of 14 experiments in the warm room the maximum vasoconstrictor response to smoking was less than the maximum vasoconstrictor response to cooling the room from 83° to 68°F. (averages 61.7% and 27.7% of the warm room control values respectively).

The striking similarity of the vasoconstrictor responses to smoking in the warm and the cool room and before and after abstinence from tobacco suggests that different control levels of vasomotor activity do not alter significantly the vasoconstrictor effects of smoking cigarets. Under the conditions of this study smoking was a less intense vasoconstrictor stimulus than cooling the environment from 83° to 68°F.

The Hematocrit of the Human Forearm Capillary Bed

By *Lawrence S. Lilienfield, Renato D. Kovach, Frank A. Porfido and Edward D. Freis.* Cardiovascular Research Laboratory, Georgetown University Medical Center and the V. A. Hospital, Washington, D. C.

The discrepancy between the hematocrit as measured in Wintrobe tubes, and the total body hematocrit as calculated from total red cell mass and total plasma volume determinations, has been assumed to be due to a low hematocrit in the capillaries. Fähreus' classic experiment with fine glass tubes has led to the belief that the low hematocrit in capillaries is due to axial streaming of red cells.

Previous studies reported from this laboratory have shown insufficient axial streaming effects in the human lung to account for any significant lowering of the capillary hematocrit in that organ. A similar technic has been applied to study the forearm capillary beds in 8 human subjects.

Following simultaneous injection into the brachial artery of Cr^{51}-tagged red cells and I^{131}-tagged albumin, blood was collected continuously in 5-second samples for 2 minutes from an antecubital vein. The Cr^{51} activity of washed red cells and the I^{131} activity of the plasma in each sample was plotted logarithmically against time, and the mean circulation times (MCT) of the red cells and plasma determined.

The ratio of red cell MCT to plasma MCT averaged .96 ± .04 in these patients. From the ratios it was possible to calculate directly the forearm circulating hematocrit without flow measurements. The forearm hematocrit averaged 98 ± .03% of the large vessel (Wintrobe tube) hematocrit.

These data indicate that axial streaming of red cells does not occur in the forearm capillary beds to a sufficient extent to lower the capillary hematocrit significantly. If a low capillary hematocrit does exist, it may be due to an excess of plasma in intermittently closed vessels, or to a slowly circulating extravascular albumin space which can be measured only by equilibration rather than by single circulation technics.

Peripheral Vascular Reactions in Experimental Shock due to Endotoxin

By *Robert P. Gilbert and Paul Gordon.* V. A. Research Hospital, Chicago

The peripheral vascular system is thought to play an important part in the hemodynamic changes

of endotoxin shock. In an attempt to elucidate this, the over-all and segmental resistance changes have been studied in the dog's forelimb by the method of Haddy et al. before and after the administration of endotoxin. Constant flow was maintained with a pump.

The intravenous injection of endotoxin caused a brief fall in resistance which was succeeded by a marked rise lasting 1–2 hours. The venous gradient rose moderately in 10 out of 12 dogs. These reactions were more marked than those seen during a comparable degree of hypotension from bleeding, although there specificity has not been established. Procaine block has not always prevented them.

Because of the possible role of adrenergic substances the response of limb resistance to graded doses of norepinephrine was measured. The perfusion pressure increment was diminished after endotoxin, but norepinephrine still caused the total resistance of the limb to reach levels similar to those attained during the control period, since over-all limb resistance had increased after the endotoxin. By 45–60 minutes there was a true decrease in norepinephrine responsiveness which could not be significantly altered by the infusion of hydrocortisone. Similar changes were shown after bleeding.

It seems probable therefore that: (1) there is no relaxation of the 0.5 mm. or larger veins of the dog's forelimb after endotoxin, (2) that there is increased vasomotor activity, (3) that there is no early loss but a later decrease in norepinephrine responsiveness, and (4) that hydrocortisone does not alter the late loss of responsiveness. It seems unlikely that loss of norepinephrine responsiveness is important in the pathogenesis of experimental endotoxin shock.

Studies of Headache: Reactivity of Bulbar Conjunctival Vessels during the Migraine Type of Headache and Muscle Contraction Headache

By *Adrian M. Ostfeld and Harold G. Wolff.* Study Program in Human Health and Ecology of Man, Departments of Medicine (Neurology) and Psychiatry, New York Hospital–Cornell Medical Center, New York City.

Slit-lamp examination of bulbar conjunctival vessels was performed in 48 headache subjects and 14 controls on approximately 300 occasions, and over 400 photographs were made.

During migraine headache there predictably occurred, largely on the side of headache, dilatation of arterioles and venules, increased numbers of patent capillaries, conjunctival edema and local burning pain. On topical application of serial dilutions of isotonic buffered solutions, arteriolar and capillary sensitivity to levarterenol decreased, and sensitivity to acetylcholine increased. Topical cortisone increased sensitivity to levarterenol. After intravenous ergotamine tartrate or levarterenol, vasodilatation, pain and edema promptly terminated and the bulbar conjunctival vessels returned to the premorbid state. During migraine attacks, the predictable occurrence of large and minute vessel dilatation, pain and lowered deep-pain thresholds and local edema supports the inference that minute vessel dilatation permits leakage into tissue of a substance which lowers pain thresholds and enhances pain due to artery dilatation. That histamine is a relevant substance is unlikely. Whereas pretreatment with intravenous benadryl and topical tripelennamine blocked, respectively, histamine-induced headache and conjunctival vasodilatation, these agents affected in no way the subsequent headache and conjunctival vasodilatation when given to patients acutely anticipating migraine headache attacks.

During muscle contraction headache there were predictably bilateral arteriolar constriction, fewer visible capillaries, decreased reactivity to acetylcholine and increased response to levarterenol. This vascular pattern was reproduced by intravenous levarterenol, was unaffected by hexamethonium blockade, and after cervical sympathectomy. Such headache was transiently diminished by intravenous Regitine and by amyl nitrite inhalation. The predictable occurrence during frontal muscle contraction headache of bulbar conjunctival ischemia concurrently with large vessel constriction supports the thesis that local skeletal muscle ischemia of partly humoral origin is relevant to pain mechanism during sustained skeletal muscle contraction about the head.

The Rationale of Venous Occlusion Plethysmography

By *Paul F. Formel and Joseph T. Doyle.* Department of Medicine and Cardiovascular Health Center, Albany Medical College, Albany, New York.

The validity of the venous occlusion method of plethysmography rests upon the assumptions that for an indeterminate period the arterial inflow into the occluded segment is unaltered, the venous outflow is completely interrupted and the impounded blood causes the occluded segment to swell proportionally. These assumptions have been generally accepted without having been systematically investigated. The following studies were therefore undertaken.

A modified water displacement plethysmograph with a strain-gage sensing unit was used. The venous pressure within the occluded forearm segment, the brachial arterial pressure and the occluding cuff pressure were recorded simultaneously with the plethysmogram.

Visual integration of the slope of the plethysmogram demonstrates that the rate of arterial inflow is essentially unaltered until the venous pressure in the occluded segment reaches a level of 35–40 cm.

H_2O. Thereafter, inflow appears to fall off in proportion to the diminution in the arteriovenous pressure gradient. These data suggest that the arterial inflow into the occluded segment is initially not significantly changed, and that the venous outflow is completely or partially impounded at a constant rate.

When radioiodinated serum albumin is injected into a dorsal vein of the hand, specific activity in the arm just proximal to a venous occluding cuff rises abruptly at the moment when the venous pressure in the occluded segment equilibrates with the cuff pressure. It is deduced that until this moment, the occluding cuff fairly completely obstructs the venous return.

If the hindleg of an experimental animal be excluded by a crushing tourniquet from the systemic circulation, except for the femoral artery and vein, the increase in the volume of the leg following obstruction of the femoral vein is proportional to the metered arterial inflow.

It is felt that these observations satisfactorily validate the venous occlusion method of plethysmography.

Venous Pressure in the Hand

By *John M. Wallace.* Durham, North Carolina

Relatively little is known of the role of small veins in the circulation. That they may play a significant part was emphasized recently by Haddy, Richards, Alden and Visscher who measured in dogs pressures in veins of 0.2–0.5 mm. diameter and found them in certain instances to exceed plasma colloid osmotic pressure. We set out to repeat such measurements in humans, without utilizing venous cutdowns. However, we have not succeeded in manipulating a catheter into veins that small; therefore, this report deals with the smallest ones which were routinely catheterized.

Five normal subjects were studied. A 21-gage needle was inserted toward the fingers in a dorsal hand vein and a semistiff catheter threaded in. The tip always stopped over a proximal interphalangeal joint or in the interdigital webbing, and could not be advanced farther, presumably because of valves or venous tortuosities. Another catheter was placed in a somewhat larger hand vein and pressures were recorded through Lilly manometers. Records were made of the responses to venous and arterial cuffs and to water baths of 10–15°C. Correction was made for hydrostatic factors in the given figures.

Pressures in both veins ranged from control values of 14–26 mm. Hg to 17–44 mm. in the cold hands. In all cases average pressures rose in the cold, in 3 of the 5 more so in the smaller than in the larger veins. In an additional subject, a 22 mm. Hg rise developed in a cooled vein with little rise in a nearby slightly larger uncooled one. Haddy commented that a characteristic response of small vein pressure is a sharp fall when the major limb artery is occluded. In modified form, we saw this in cooled veins in several instances. Abnormal responses to cuffs were observed in single patients with scleroderma and postural hypotension.

A Technic for Measuring Changes in Venous Tone, with Demonstration of a Defect in Portal Cirrhosis

By *John J. Duggan, Howard Albright and Thomas J. Murphy.* V. A. Hospital, Syracuse, and the Department of Medicine, State University of New York, College of Medicine, Syracuse.

A method has been developed for the measurement of acute changes in tone in unobstructed peripheral veins in man, and applied in normals and in certain disease states. Under conditions of constant intraluminal pressure, changes in vessel diameter as determined by serial caliper measurement have been used as an index of changes in tone.

By encircling the vein with procaine, 2 segments may be observed. The vein proximal to the procaine block serves for the demonstration of neurogenic responses. As demonstrated previously, the vein distal to the procaine is functionally denervated. This distal segment serves both as a control for neurogenic reactions and as an indicator for responses to circulating vasoactive substances. Neurogenic constriction was demonstrated in response to the cold pressor stimulus, hyperventilation, the initiation of exercise and tilting from the horizontal toward the vertical. Diminution in neurogenic tone was produced by immersion of the opposite hand in warm water. Amyl nitrite inhalation, 5% CO_2 breathing and total body-heating produced dilatation in both segments, while norepinephrine produced constriction in both. The absence of neurogenic venomotor response in severe diabetic neuropathy was confirmed.

A striking finding was the absence of reflex venomotor responses to cold and hyperventilation in 13 patients with severe portal cirrhosis. This lack of response occurred in the absence of impending coma or of evident peripheral neuropathy, and despite venous contraction on local stimulation by trauma, cold or norepinephrine. All of these patients showed spider angiomata and palmar erythema, many had red fingertips, and 2 had clubbed fingers.

Peripheral venous responses to reflex and circulating stimuli may be demonstrated by a simple technic. Depression of venomotor tone is another element in the disturbed circulatory pattern of portal cirrhosis.

Pathogenetic Mechanisms in Venous Thrombosis

By *Stanford Wessler, Leopold Reiner and Jonathan D. Ballon.* Departments of Medicine and Pathol-

ogy, Beth Israel Hospital and Harvard Medical School, Boston (Aided by grants from the American Heart Association and the U. S. P. H. S.)

In dogs, the systemic infusion of canine serum produces a temporary hypercoagulable state during which massive thrombosis can be regularly induced with minimal endothelial injury in areas of retarded blood flow. Sequential histopathologic studies have revealed that these thrombi are: (1) indistinguishable at first from postmortem clots, (2) undergo spontaneous changes in fragility, (3) do not adhere to the underlying vein wall until the fourth day, and (4) may be loosely attached for days to weeks after intial adherence to the vascular endothelium. Among the observed morphologic alterations in clot structure, a most striking finding was the frequent occurrence of fresh hemorrhage within thrombi one or more weeks of age. With hemorrhage, thromboplastic elements may be released and serum (which possesses striking clot promoting qualities) elaborated. Additional clotting may thus be induced consequent to the process of clot organization itself.

These experiments provide insight into pathogenetic mechanisms in thromboembolic disease in man. They have suggested the following formulation: (1) in patients with idiopathic intravascular clotting, there is a hypercoagulable state that predisposes to thrombosis; (2) during this abnormal state, a clot can be initiated and then potentiated by a degree of vascular stasis that would not *by itself* result in thrombus formation; (3) among these patients with idiopathic intravascular clotting, hypercoagulability and vascular stasis may be systemic or local, transient or prolonged, or recurrent. This conceptual framework supports a rational basis for the treatment of many patients with recurrent venous thrombosis and pulmonary embolism in which therapy is predicated first upon effective neutralization of hypercoagulability and, second, upon a reduction in vascular stasis.

Roentgenographic Recognition of the Azygos Vein and the Differentiation from Peritracheal Adenopathy

By *William H. Anderson.* Department of Internal Medicine, Miner's Memorial Hospital, Harlan, Kentucky.

Several instances wherein a patient has been subjected to exploratory thorocotomy for a presumed diagnosis of mediastinal tumor or adenopathy have been recorded. Only an azygos vein in the region of the presumed tumor was found. It has also been suggested that when the azygos can be seen prominently on an x-ray of the chest, venous congestion is present. In the present study, the azygos vein was seen in 100 of 187 PA tomograms. The vein averaged 1.4 cm. in its greatest transverse diameter and was seen for a distance of 3 to 5 cm. in the PA plane. The absolute level at which the vein could be seen was found to vary with the thickness of the chest; but it was most commonly seen at the 8 to 11 cm. level from the table top.

Changes in intrathoracic pressure, as measured at the mouth by means of a manometer, of the magnitude of 80 to 140 mm. Hg produced a change of between 28 and 58% in the transverse diameter of the azygos vein. The vein was largest with negative and smallest with positive manometer pressures. No conclusions should be drawn from the size of the vein, or change in size of the vein, regarding the venous circulation unless the approximate intrathoracic pressure is known.

Thus, the azygos vein is to be differentiated from adenopathy or tumor in that it is located at the site of origin of the right main stem bronchus from the trachea, measures an average of 1.4 cm. in its greatest transverse diameter, is 3 to 5 cm. in depth in the PA plane, and changes significantly in size with changes in intrathoracic pressure.

ECOLOGY

The Distribution of Illness in a Homogenous Group of Adult Men

By *Lawrence E. Hinkle, Jr., Ruth H. Pinsky, Irwin D. Bross, Robert P. Schaen and Normal Plummer.* Study Program in Human Health and the Ecology of Man, Departments of Medicine and Psychiatry, New York Hospital—Cornell Medical Center, New York City.

Previous studies have indicated that men exhibit differences in their susceptibility to illness in general, in addition to their differences in susceptibility to specific illnesses.

To investigate this, 226 randomly selected adult men similar with regard to cultural, social and economic background, education, occupation and area of domicile, all of whom intermingled freely with a large metropolitan population in an area of good sanitation, were studied in order to ascertain every illness which had occurred in each man during a 20-year period from his early 20's to his early 40's. Each member of the group was healthy at the beginning of this period. For each man there was available a record of his prior health, his initial physical condition, his attendance at work, and his condition at the time of examinations made periodically during the observation period. There was a description of every episode of illness which had taken place during this time, with reports of examinations and

diagnostic procedures carried out at the time of its occurrence.

(1) The distribution of sickness episodes among these men cannot be explained by assuming that all of the men had the same probability of becoming ill. Some men had much more and some much less than the amount of illness to be expected, if this were true.

(2) The difference cannot be explained by differences in morale, attitudes and behavior.

(3) Men having the greater amount of illness exhibited illness in a large number of body systems.

(4) Those having the most frequent minor illnesses had the most frequent major illnesses also.

(5) Those having the greatest number of disturbances of feeling state, thought and behavior were among those having the greatest number of bodily illnesses.

(6) There was a positive correlation between the number of sickness episodes experienced by each man during the first 5 years of observation and those he experienced during the subsequent 15 years.

These findings are consistent with the hypothesis that members of the group exhibited differences in their general susceptibility to illness during the observation period.

Concepts of the Epidemiology of Sarcoidosis, Based on a Review of 1194 Cases in Veterans with Special Reference to Geographic Ecology

By *Martin M. Cummings, Edward Dunner, Richard H. Schmidt, Jr. and John B. Barnwell*

The present report is based upon a review of 1194 cases of sarcoidosis seen in 172 V. A. hospitals between 1949 and 1954. Information concerning age, race, sex, occupation, place of birth and place of initial hospitalization was reviewed in an effort to detect epidemiologic patterns which might afford clues to etiology.

The hospitalization rate for white World War II veterans with sarcoidosis was 3.3 per 100,000 and 40.0 for Negro veterans. The comparative rates of sarcoidosis of white veterans by birthplace revealed that the highest hospitalization rates occur among veterans born in Connecticut, Rhode Island, Georgia, Arkansas, North Dakota, Minnesota, Massachusetts, Alabama, Maine and Virginia, in order of decreasing frequency. The hospitalization rates for Negro veterans was 20 times greater than in white veterans, and showed a preponderance of cases born in the Southeast.

A study of the geographic distribution by birthplace of all veterans extends the distribution pattern of the disease to areas of the United States not previously considered to be endemic. Correlations between the distribution of sarcoidosis in veterans and certain ecologic factors suggests that some aspect of the forest distribution in the United States may be an important environmental factor responsible for the geographic concentration of the disease.

Observations in a "Control" Group of Patients in Psychosomatic Investigation

By *Solomon Papper and Juanita Handy*. Medical Service and the Social Service Department, Boston V. A. Hospital, and the Departments of Medicine, Boston University School of Medicine and Tufts University School of Medicine, Boston.

In order to make controlled observations of the social and emotional aspects of certain "psychosomatic" illnesses, patients with viral hepatitis were studied as a "control" group. Each of 25 consecutive cases of hepatitis had approximately 3 hour-long interviews with 1 author (S.P.) while social service data were accumulated independently by the other (J.H.).

Observations in this "control" group include the following: (1) At least 8 of the 25 grew up in "broken" homes. (2) 12 demonstrated sufficient drive and ambition to have attended school while holding a part-time or full-time job. Failure to achieve goals was common in this group. (3) 7 of the 17 married subjects had either been separated from their wives or had seriously considered separation. (4) The group exhibited personality patterns conforming to those described in several "psychosomatic" illnesses. (5) Mother was the dominant parental figure more often than the father. (6) Of great interest is the observation that 18 of 25 patients had distinct histories of various kinds of acutely disturbing emotional experiences 4–9 weeks before the onset of hepatitis.

In order to control the "control" group, particularly with regard to antecedent distressful episodes, 10 patients with acute appendicitis and 10 with pneumonia were studied with comparable findings.

These observations are subject to two interpretations: (1) acute emotional distresses may be important determinants of "resistance" in a variety of disorders, or (2) such episodes are part of the living process and are chance occurrences only temporally related to the onset of organic illness.

It is also apparent from the data that control observations in any patient population are as important in "psychosomatic" research as in other investigative areas.

EDUCATION

Adapting the Group Discussion Technic for Use with Large Classes

By *N. J. Cotsonas, Jr., R. J. Kaiser and H. F. Dowling.* University of Illinois Medical Service, Cook County Hospital and University of Illinois College of Medicine, Chicago.

Among the valuable features of clinical clerkship teaching are student participation, the opportunity to put knowledge to use, and learning through discussion. In the fall quarter of 1954, we began a series of student conferences in which we attempted to incorporate these desirable features. Effective use of the group discussion technic presented a problem because we were dealing with classes of about 50 students. We shall discuss our solutions of the problems encountered:

(1) *Format:* Presentation of an actual (common) clinical problem by the clerk in such a way that the history, physical examination and routine laboratory work on admission serve as facts available to all students for use in constructing a differential diagnosis and outlining a program of management.

(2) *Teacher Orientation:* The primary goal is to provoke responsible student participation. The emphasis is on *utilization* of knowledge (gained elsewhere), not the introduction of new information.

(3) *Student Orientation:* A continuing process emphasizing the value of oral communication and the experience to be gained from projecting oneself into the role of physician. Each student who participates discharges his responsibility to the group because his comments may uncover not only information and understanding, but misinformation and misunderstanding which may have been shared by a sizable part of the group.

(4) *Technic:* presentation of the value of conference planning, including the incorporation of guest teachers, the functions of an "outside director" in educating faculty to the technics, methods of initiating, controlling and directing discussion within a large group and the most useful methods of handling misinformation.

(5) *Evaluation:* Presentation of student and faculty opinion regarding these conferences, as obtained from questionnaires completed anonymously.

Conference and Panel Teaching in the Medical Curriculum as a Form of Interdepartmental Teaching, with Special Comments on the Teaching of Therapy

By *Daniel H. Labby.* Department of Medicine, University of Oregon Medical School, Portland

The course in medical therapy at the University of Oregon Medical School has offered a partial and unexpected solution to the curriculum problem of communication across interdepartmental and disciplinary barriers. It has become a means for evaluating basic concepts in therapy, for open discussion of new drugs, and for judging the applicability of research data as they apply to the scientific practice of medicine. Up to 1951, no formal course in therapy was available. The basic approach was considered fundamental and implicit in all that was taught, but the major emphasis had been given to the clinical sciences and the development of skill at the bedside in diagnosis. Therapy was considered relatively secondary, once an accurate diagnosis was established. As it has evolved, this course has permitted basic science people and clinical specialists to operate before senior medical students in a common arena. The class faces a mixed panel of specialists, representing basic scientists from the medical school faculty, the full time clinical staff, and practitioners.

The basic plan has been to give broad coverage to well-focused problems, and the department of pharmacology has been asked to cosponsor and participate, especially in those sessions involving questions of drug therapy. A moderator acts not only to direct discussion among the members of the panel, but also to project the discussion into the audience in a hope of eliciting questions from the students and staff. The students are exposed to an interdisciplinary and interdepartmental function in which scientific medicine is broadly viewed as a phase of biology without reference to artificial barriers or departmental lines. For example, the panel that considered "Exploring the Rationale for the Practice of Allergy" consisted of a practicing allergist, a serologist and a biochemist, and was moderated by a member of the full-time faculty in internal medicine. Other panels have been composed completely of students and moderated by staff members; still others have had students sitting in with staff members as "temporary" experts. The subject coverage has been broad; in addition to specific problems of therapy, industrial medicine, forensic medicine, and marriage counseling have been covered by a variety of specialists including social service workers, business executives and sociologists. This has served to acquaint the students with various agencies active within the community, and to hear open discussion with medical men of mutual problems.

The broad base upon which this course is conceived allows for the freest kind of operation, and is limitless in range. It has offered another opportunity at the university for the interplay of the basic scientist and clinical faculty, as well as social scientists at the teaching level, and has acquainted both with the problems of each.

Improving Teaching on Ambulant Patients

By *Kerr L. White and William L. Fleming.* Departments of Preventive Medicine and Medicine, University of North Carolina.

Ambulant patients afford teaching opportunities not always available on hospitalized patients, e.g., (1) experience in diagnosis at the earliest stages of disease; (2) proximity to the points at which preventive measures are realistically applicable; (3) a broader view of patients' problems in the context of their family, work and community environment; (4) experience with minor emotional and functional disorders; (5) longer periods for observing disease processes and physician-patient relationships; (6) the pedagogic advantages of assigning senior student-physicians new "unknown" patients with general medical disorders.

Problems involved in realizing these advantages concern both teachers' attitudes and experiences and organizational patterns, e.g., (1) the neglected status of out-patient teaching in many hospitals; (2) time limitations for teacher-student consideration of detailed aspects of diagnosis, pathologic physiology and management; (3) the anxiety and insecurity specialists experience when teaching on "general" ambulant patients; (4) the frustration and anxiety experienced by some clinicians when confronted by unfamiliar emotional and soicoenvironmental aspects of illness; (5) the difficulties of arranging special diagnostic studies on ambulant patients; (6) the maintenance of a sound theoretic and clinical balance in considering not only disease processes but also the patients who experience the diseases.

In the University of North Carolina General Clinic, members of the departments of medicine, preventive medicine, psychiatry and part-time practicing physicians are the students' preceptors in a "core" clinic, supported by subspecialty clinics, and augmented by participation of a sociologist, a social worker and a public health nurse. Teaching conferences include: (1) seminars on the natural history and preventive aspects of disease, (2) clinical physiologic conferences, (3) daily teaching rounds, (4) history taking and interviewing technics, (5) electrocardiography, (6) home health service problems, (7) medical emergencies, (8) x-ray diagnosis.

Sufficient progress with our out-patient program over a 3-year period encourages us in the belief that our experiences may be useful to others.

Some Methods and a Rationale for Sociologic Studies in Medical Education

By *George G. Reader, Renee Fox, Mary Goss and Gene Levine.* New York Hospital–Cornell University Medical School and Bureau of Applied Social Research of Columbia University, New York City.

Since the educational process in medicine in part involves exposure of the student to a particular social context—the medical school and the hospital—for a period of 4 years, in the course of which he develops a new role—that of physician—social scientific technics of investigation and application of sociologic theory may be expected to help explain the relevance of what occurs to the student during that period to what he learns about medicine. Introduction of a teaching program in comprehensive medicine at Cornell Medical College provided the impetus for a study of the medical school environment and of the effects of the new program. This study has now been carried on for 4 years, and various methods of sociologic research have been used.

In order to know whether change in attitudes, values or information takes place as a result of participation in the comprehensive care and teaching program, an attitude questionnaire was constructed and administered to students in May of 1952 and, with appropriate revisions, has been administered since then each December and May to students at Cornell. Comparisons of data from the questionnaire before and after exposure to the program, and during the course of the entire medical school experience, are possible as a result.

Another technic extensively used in the studies has been that of participant observation. Throughout the years an observer has been at the New York Hospital–Cornell Medical College from 2 to 3 days each week. In formal meetings, the observer took notes on the spot; in less formal situations notes were made later and in private. From these observations an analysis of the social context in which the medical students learn is possible.

An extension of the participant-observer technic has been the use of student diarists who have acted as observers, being paid for recording their observations and being interviewed weekly by a sociologist. This has extended the range of observations made not only of the social context of the medical school, but also of the students' reaction to it.

Because attitudes of the faculty also represent a vital part of the medical student's environment, they too have been subjected to systematic study. Interviews have been carried out with a random sample of the entire clinical faculty to determine whether student attitudes may be related to those of their teachers.

Findings from these various methods of observation can be shown to have scientific validity, and permit a topograhic map to be drawn on which the mountains and valleys and other features of the medical terrain can be plotted and their significance for the student ultimately evaluated.

A Pattern for Instruction in Occupational Medicine

By *Jean S. Felton.* Departments of Medicine and Preventive Medicine and Public Health, University of Oklahoma School of Medicine, Oklahoma City.

The introduction of a new specialty into an established curriculum offers opportunity for varia-

tion in teaching design. At the University of Oklahoma 22 lectures are given in the fourth year, sessions heavily studded with visual aids, and covering medical programs in industry, job placement, health hazards, control measures, workmen's compensation and mental health, dermatoses, and case-finding technics in industry. In the Health Service, established for the preventive care of students and employees, each senior spend 2 mornings in the study of the employed physically handicapped. In teaching conference (3 to 4 students), the patients are reviewed through group interview, in the light of job placement, work stresses and needs for continuing medical surveillance. A 4-hour visit to the world's largest air maintenance depot demonstrates industrial hygiene control and medical department management. Attendance by the instructor in Medicine Clinic teaching conferences permits a dual understanding of the patient's medical and employment problems. In the first year, an hour's historical review provides initial exposure to medicine of industry, and sophomores have 6 hours of lecture, slides and film.

Pertinent to this curricular segment is the experience given entering-freshmen who receive an *unhurried complete* physical examination in the Health Service, as the result of a joint effort of the full-time faculty of the department of medicine. The findings from this, psychologic tests, and laboratory procedures, are interpreted in a conference with each student, and plans are made for follow-up study. The 5-hour investigation of a *well* person thus becomes a lived-through procedure for the student—what is taught is exemplified by local practice. Exposure to the Work Evaluation Clinic adds interest in work motivation. Lectures to students in physiotherapy, and duty for student nurses in the Health Service and at an Air Base represent teaching extensions to other personnel.

Adventure in Pedagogy

By *George E. Miller*. University of Buffalo School of Medicine, Buffalo

Good teachers are reputed to be born, not made. On the basis of a 2-year preliminary study the impression was gained that a less risky method of identification and preparation of able medical instructors might be employed.

To test this hypothesis a seminar for 13 representatives of several preclinical and clinical disciplines was established for discussion of the teaching-learning process during 10 weekly 2-hour periods under the leadership of a student of the science and master of the art of pedagogy recruited from the College of Arts and Sciences.

The several faculty members approached this opportunity with varying degrees of interest. One withdrew at the end of the first session and 2 others attended irregularly. The remaining 9 underwent a unique and somewhat painful self-examination which led them to a recognition of their general unfamiliarity with: (1) what constitutes learning, (2) the ways in which learning occurs, (3) the influence of teachers upon the learning process and (4) the motivation of teachers.

Perception of these blind spots made it possible for the participants to develop a more sensitive vision of: (1) the professional role of the teacher, (2) the emotional needs of students and instructors, (3) the measurement and quality of learning and (4) the nature of compromise.

The subtle change in attitudes which resulted from these discussions was accompanied by significant change in teaching practice. Whether this change represented improvement could be the subject of lively debate. In the belief that it did, the initial study is being expanded into a more comprehensive program for the preparation of medical teachers.

An Evaluation of the Use of a History Form in a General Medical Teaching Clinic

By *Thomas N. Roberts and Clinton G. Weiman* New York Hospital, New York City

The desirability and feasibility of using a history form in a general medical teaching clinic for fourth year students was investigated. The form used in this study was completed by the student during the interview and included sections on the family history, past medical history, systemic review and personal history. The use of the form did not reduce the time necessary for obtaining the history but did save time in the recording of the history. Use of the form generally resulted in a more complete recorded history. The great disadvantage of the form was that it seemed to interfere with the student physician-patient relationship. This defect is dependent in part upon the adaptability and interviewing skill of the individual student and in part on the type and structure of the form.

Experiences with Terminal Care in a Home Care Teaching Program

By *L. Sonkin*. New York City

This report will present a summary of experience derived from the supervision of medical students participating in home care to terminally ill patients in the New York Hospital–Cornell comprehensive care and teaching program.

Home care was provided by a team consisting of a fourth year medical student who assumed the most active role, comparable to that of the ward intern, a full-time member of the department of medicine who supervised the student, a nurse and a social worker. Each student was assigned at least 1 home care problem during all or part of his 22½-week course in comprehensive care.

During the 2-year period from July 1953 through June 1955 88 patients received home care, 17 of whom were considered to be terminally ill.

A careful record of student time spent on home care of dying patients during the second year revealed a range of 40 minutes to 3 hours and 40 minutes a week. The cases which required most time per week were usually the more acutely ill with the shortest life expectancy. Thus, no patient who required more than 2 hours of student time weekly survived for longer than 6 weeks, and students were not required to spend an unreasonable amount of time with undue distortion of the remainder of the curriculum.

A questionnaire submitted to the students at the completion of their home care experience indicated, in general, a more favorable response to terminal care cases than to other types of home care problems.

Terminal home care seemed to provide an important type of experience which has not heretofore been available to medical students. It provided an especially fertile field for the student to gain experience in developing a sound physician-patient family relationship. The student could gain first hand experience with agencies such as Visiting Nurse Service, National Cancer Foundation, Department of Welfare, private nursing registries and nursing homes. Moreover, an ample opportunity was provided for the continued observation of a variety of pathologic states with all of the laboratory facilities of a large teaching hospital. The students were frequently able to obtain experience in the care of wounds, paracentesis, thoracentesis, and other procedures equivalent to those performed on in-patients. They participated in the writing of death certificates and obtained hospital autopsies on 50% of the patients who died. Finally, the students were provided an opportunity for developing a mature philosophy concerning the care of terminally ill patients.

The Problem of Graduate Medical Education

By *R. I. McClaughry*. Providence Hospital, Detroit

At the beginning of the 20th century, the state of undergraduate medical education in the United States was indeed precarious. The danger lay not in an insufficient number of medical schools, but rather in the proprietary nature of most of these schools. Medical schools were operated in large part by groups of persons more interested in the tuition paid by the medical students than in the quality of the education these students received. This problem was squarely met and satisfactorily solved. Every medical school now granting the degree of Doctor of Medicine in the United States is voluntarily meeting the high standards maintained by the accrediting agencies.

On entering the second half of this century, we face an equally great challenge in the area of graduate medical education. We have gone through a period of rapid development in medical knowledge. It is no longer possible for a physician to be adequately prepared for the responsibilities of practice on the completion of his internship. There has been developed a new structure in medical education to provide the additional practical experience necessary. This field is designated "graduate medical education," and it is carried on almost exclusively in residency programs in general and special hospitals.

A distinct parallel exists between the proprietary interests of the medical schools in 1910 and the hospitals in 1956. The current equivalent of the tuition fee is that of low-cost professional services to patients. Variations of this same situation can be seen both in private and charity hospitals. Our problem can be succinctly stated to be that of elevating the level of graduate medical education while simultaneously maintaining the best possible patient care. Parallels also exist between the steps taken at the undergraduate level and some of the possible solutions to the present problem.

ENDOCRINES AND METABOLISM

The Serum Pattern of Thyroid Hormones in Various States of Thyroid Function

By *Walter L. Arons and Jerrold D. Hydovitz*. Department of Medicine, University of Pennsylvania School of Medicine and the Medical Service, Hospital of the University of Pennsylvania, Philadelphia.

Radio-paper chromatography, following the administration of I^{131}, has been carried out on the peripheral serum of 9 euthyroid patients, 13 hyperthyroid patients, 5 subjects with thyroid malignancy and in 2 individuals following the administration of thyroid stimulating hormone (TSH). Paper chromatography of each serum sample was carried out in both butanol dioxane ammonia and tertiary amyl alcohol ammonia solvent systems. In none of the euthyroid patients could evidence of radioactivity be found anywhere except in the thyroxine area. By contrast, in the thyrotoxic group, in addition to the constant thyroxine activity, significant radioactivity has also been noted in the triiodothyronine area in 10 cases, in the diiodotyrosine spot in 5 cases, and in the monoiodotyrosine area in 2 individuals. In these hyperthyroid individuals, triiodothyronine activity could be detected

in the serum within 6 hours after the administration of I^{131}. One functioning metastatic thyroid malignancy has been shown to be capable of producing thyroxine, triiodothyronine and diiodotyrosine. In a euthyroid patient, the administration of thyroid-stimulating hormone was followed in approximately 30 hours by an increase in the serum level of radioactive triiodothyronine. Such an increase in triiodothyronine did not occur following the administration of TSH to a hyperthyroid subject.

Relationships between Clinical Severity of Hyperthyroidism and Test Results

By *Alvin L. Schultz and Leslie Zieve.* Department of Medicine and Radioisotope Service. V. A. Hospital and University of Minnesota, Minneapolis.

A quantitative clinical severity score was derived by rating the most important symptoms and signs of hyperthyroidism on a 6 point scale, weighting the items on the basis of their clinical importance, and combining the weighted ratings to get a single score. Such a score enhances the likelihood that different clinicians at different institutions mean the same things when speaking of mild or severe hyperthyroidism. In addition, it allows an evaluation of the extent to which various tests reflect clinical severity.

In 53 hyperthyroid patients correlations between the clinical severity score and 9 test variables varied from 0.15 to 0.61. The highest correlations were with the thyroid clearance (0.61), thyroid uptake in 3 hours (0.59), rate of uptake of dose by the gland (0.57), and BMR (0.44). Correlations with the chemical protein-bound iodine, 24-hour uptake, cholesterol, protein-bound radioiodine, and conversion ratio were 0.30 or less in decreasing order. The best linear combination of all 9 tests, for purposes of predicting clinical severity, raised the correlation to only 0.74. Two tests alone, the thyroid clearance and BMR, were equally effective in predicting clinical severity, yielding a multiple correlation of 0.72.

Adrenocortical Function in Myxedema and Hyperthyroidism

By *Gerald A. Williams, K. R. Crispell and William Parson.* Department of Medicine, University of Virginia, Charlottesville.

There is a prevailing concept that adrenocortical function is decreased in patients with myxedema. This is manifested by decreased urinary 17-ketosteroids, failure of ACTH to produce a fall in eosinophils, and low or low-normal urinary 11-oxycorticoids. The urinary 17-ketosteroids have also been reported to be low in patients with hyperthyroidism.

Previous studies from our laboratory have shown that patients with myxedema have an abnormal response to a water load, not responsive to cortisone but corrected by thyroid. The circulating plasma level of 17-hydroxycorticoids before and following the intravenous injection of ACTH (Jailer method) was used to determine adrenocortical function. In this way not only adrenocortical function but also adrenocortical reserve was determined.

Four patients with untreated spontaneous primary myxedema of 3 to 10 years duration were studied. The fasting 17-hydroxycorticoid level was within normal limits. After ACTH stimulation, 3 of the patients had values well within normal limits, whereas 1 patient had a value slightly below normal. A repeat study of one patient after 12 days of l-triiodothyronine again revealed normal fasting and post-ACTH plasma levels. This patient had low urinary 17-ketosteroid levels which did not rise during this period of therapy. This same 17-ketosteroid pattern was found in 1 other patient treated for 5 months on whom plasma 17-hydroxycorticoid levels were not determined.

Two patients with untreated hyperthyroidism were similarly studied. In both patients the fasting plasma 17-hydroxycorticoid levels and the post-ACTH levels were within normal limits. Urinary 17-ketosteroids were determined on 1 of these patients and were within normal limits.

The studies thus far indicate that the adrenocortical function of both myxedematous and hyperthyroid patients, as determined by plasma 17-hydroxycorticoid levels before and after ACTH, is within essentially normal limits.

A Rapid Method for the Concentration and Determination of Urinary Iodide (I^{127}): Application to Thyroid Functional States

By *Harold L. Helwig, William A. Reilly, James N. Castle, Helen I. Johnson and Charles Louie.* Department of Pediatrics, University of California School of Medicine and Radioisotope Service, V. A. Hospital, San Francisco, California.

The relation of stable iodine (I^{127}) to thyroid function was investigated by a new and rapid analysis of urinary I^{127}. From measurements of urinary I^{127}, calculations were made by standard formulas of the amount of I^{127} in plasma going into the thyroid and the extrathyroidal pool. Urine specific activity was calculated; blood was assumed to be the same. Thyroid uptake of I^{131} and its urinary excretion were required.

Acidified urine was concentrated by passage through an AgCl column; the resulting AgI was treated with acidified Br_2 water, giving IO_3^-; this was purified of reducing substances and IO_3^- converted into I_2 which was quantitated (at 352 μ) by spectrophotometry.

Calculation:

$$\mu g.\ I^{127}/ml.\ urine = \frac{\mu g.\ I^{127}/ml.\ in\ cuvette}{\frac{I^{131}\ counts/sec./ml.\ in\ cuvette}{I^{131}\ counts/sec./ml.\ of\ urine}}$$

Results: for 39 euthyroid adults the range of plasma concentration was 1.6–16.4 μg./L. (mean 6.0, s.e. ±.55); range of thyroid uptake was 6.0–60 μg./6 hr. (mean 25.9, s.e. ±2.21); the range of extra thyroid pool was 0.61–6.24 μg./Kg./6 hr. (mean 2.41, s.e. ±0.70); range in urine was 30.0–602 μg./24 hr. (mean 241.2, s.e. ±25.7). For 26 hypothyroid adults, the range of plasma concentration was 0.1–20.7 μg./L. (mean 5.62, s.e. ±1.27), p 0.7; the range of thyroid uptake was 0.3–22 μg./6 hr. (mean 7.59, s.e. ±1.32), p <0.01; the range of extra thyroid pool was 0.1–8.8 μg./Kg./6 hr. (mean 2.18, s.e. ±0.894), p 0.7; the range in urine was 8.75–490 μg./24 hr. (mean 167.3, s.e., ±29.6), p 0.05. For 12 hyperthyroid adults, the range of plasma concentration was 0.26–9.32 μg./L. (mean 2.39), p <0.01; the range of thyroid uptake was 110–361 (mean 221.0, s.e. ±27.38), p <0.01; the range in extra thyroid pool was 0.86–4.4 μg./Kg./6 hr. (mean 2.47, s.e. ±0.54), p 0.9; the range in urine was 101–729 μg./24 hr. (mean 280.95, s.e. ±81.33), p 0.6.

In adult hypothyroids I^{127} uptake was decreased. In hyperthyroids there were decreased plasma levels and increased uptake and space (insufficient time for mixing in pool). Pool amount was similar in all states. Iodine poverty was found only in simple goiter (2 children, 2 adults) and 5 goitrous hypothyroid children. The latter had increased uptake.

Correlation of Clinical and Hemodynamic Studies in Patients with Thyroid Disease

By *J. S. Graettinger, J. J. Muenster, C. S. Checchia and J. A. Campbell.* Presbyterian Hospital, Chicago.

Clinical and hemodynamic data in 12 patients with hypothyroidism and in 12 patients with hyperthyroidism have been correlated. In the patients with myxedema, some of the clinical findings usually associated with congestive failure were present. Nevertheless, the low mean cardiac index at rest (1.88 ± .26 L./min./M.²) was proportional to reduced oxygen consumption; the changes in output, A-V difference, peripheral and pulmonary resistance during exercise were normal, suggesting adequate myocardial reserve.

In 7 patients with thyrotoxicosis not in heart failure clinically, a high resting cardiac index (5.8 ± 1.08 L./min./M.²) was directly correlated with increased oxygen consumption. The changes during exercise were normal. Three patients with thyrotoxicosis had clinical evidence of congestive failure and underlying heart disease. In this group the cardiac index was not abnormal at rest (3.42 ± .97 L./min./M.²) but failed to rise with exercise. In 3 other patients with both thyrotoxicosis and congestive failure, but without evidence of underlying heart disease, the cardiac output was markedly elevated (8.93 ± .97 L./min./M.²) and fell considerably with exercise. The resting values and changes of A-V difference observed in these groups were significantly different.

These observations demonstrate cardiac decompensation with a high cardiac output without evidence of an etiologic factor other than thyrotoxicosis as well as congestive failure with a relatively normal cardiac output in patients with thyrotoxicosis and underlying heart disease. Both the decreased metabolic load of hypothyroidism and the increased load of hyperthyroidism result in a change in cardiac output which is proportional to the level of oxygen consumption in the absence of congestive failure, and a normal exercise response occurs. When congestive failure is present, the fact that the cardiac load exceeds the cardiac reserve is reflected in a disproportionate relationship of cardiac output to oxygen consumption, both at rest and during exercise.

The Relation of the Thyroxine-Binding Protein of Plasma to Normal Pregnancy and to Spontaneous Abortion

By *Sidney H. Ingbar, James T. Dowling and Norbert Freinkel.* Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Service, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Despite thyroidal hyperplasia, increased PBI, and augmented thyroidal accumulation of radioiodine, pregnancy is characterized neither by clinical stigmata of hyperthyroidism, nor by elevation of BMR beyond those attributed to the growing fetus. In an effort to explain this apparent discrepancy, and in view of the changes in plasma protein concentration which occur during pregnancy, studies were made of the thyroxine-binding capacity of serum in 30 normally pregnant women. Sera were enriched with stable l-thyroxine to yield concentrations varying between 14 and 260 μg.%. The distribution of added radioactive l-thyroxine between albumin and the specific thyroxine-binding protein of serum (TBP) was assessed following filter paper electrophoresis. A highly significant increase in the thyroxine-binding capacity of TBP was noted during normal pregnancy, starting as early as the 20th postovulatory day and continuing to term.

In 21 of 22 patients with inevitable abortion, the normal gravid increase in thyroxine binding by TBP was either entirely absent or significantly diminished. Values of the protein-bound iodine were generally proportional to the degree of change in TBP. Absence of increase in thyroxine binding by TBP is probably not due to recent death of the conceptus since, (1) the normal gravid increase

persists for as long as 6 weeks postpartum, and (2) in 5 habitually aborting women a diminished TBP response was noted despite a pregnancy which was clinically normal.

Increases in the plasma's concentration of protein-bound iodine during normal pregnancy are associated with increased thyroxine-binding capacity of TBP. Whether inadequate increases in TBP in the serum of aborting women are merely secondary to abnormalities of the ova, or whether they represent deviations from the normal maternal response, and to what extent, if any, they contribute to fetal loss, remains to be determined.

Effect of Phosphate in Enhancing the Metabolic Action of Triiodothyronine

By *George Firmat, John Prunier, Rulon W. Rawson and Kathleen E. Roberts.* Memorial Center for Cancer and Allied Diseases, New York City.

We have observed that one of the thyroid hormones, triiodothyronine (T-3), even in doses up to 1000 μg., causes no measurable alteration of metabolism in dogs. The administration of this thyroid hormone to dogs pretreated with phosphate, however, leads to increased oxygen consumption, hyperthermia, tachycardia, tachypnea, and other changes which might be expected in hyperthyroid states. This finding has made it possible to carry out the experiments reported here, which were intended to study the plasma alterations associated with acute hyperthyroidism. In these studies the dogs were made hyperthyroid by the administration of 80–120 μg. of T-3 and sodium phosphate. The most significant plasma alterations which occurred are as follows: (1) a decrease in serum cholesterol, (2) a drop in plasma magnesium from control values of 1.8–2.1 to as low as 0.4–0.6 mEq./L. and (3) respiratory alkalosis. In 2 of the animals, serum transaminase (S-GOT) was measured, and there was a rise of this enzyme to 64–112 U within the period of study (control values 32–40). All of these alterations were maximum at 100–120 minutes following triiodothyronine administration, and death usually occurred within 160 minutes.

These findings confirm that phosphate enhances the action of at least one thyroid hormone, and suggest that these findings might profitably be considered in patients with elevated phosphate who are given thyroid hormone.

The Relationship of Renal Tubular Reabsorption of Phosphorus and Magnesium to Parathyroid Activity

By *A. Sigrid Gilbertsen and B. J. Kennedy.* Department of Medicine, University of Minnesota Hospitals and University of Minnesota Medical School, Minneapolis.

The immediate effect of the administration of parathyroid extract is to produce a phosphorus diuresis which is thought to be mediated by the action of parathormone to decrease renal tubular reabsorption of phosphorus. A quantitative estimate of the amount of phosphorus reabsorbed by the renal tubules can be made from measurements of the creatinine clearance, serum phosphorus and urinary excretion of phosphorus. It has been suggested that the ratio of phosphorus reabsorbed by the renal tubules per minute to the phosphorus filtered through the glomerulus per minute (TRP:GFP) may serve as an index of parathyroid activity. This ratio approaches 1.0 in the absence of parathyroid hormone and declines toward 0.0 with increased parathyroid activity.

The validity of this ratio as a parathyroid activity index has been confirmed by observations in 8 patients with parathyroid adenomas. Initially, the percentage of tubular reabsorbed phosphorus was significantly below the normal range; following removal of the parathyroid adenoma the ratio rose to normal. A lowered TRP:GFP ratio was found in 7 of 8 patients with osteolytic bone disease due to metastatic cancer or multiple myeloma; in these patients continued reabsorption of phosphate from bone was postulated to provide the stimulus to the apparent increased parathyroid activity. Patients with senile osteoporosis, renal calculi and nephrocalcinosis without other evidence of parathyroid disease manifested no decrease in the per cent of tubular reabsorbed phosphorus.

Simultaneous estimates of tubular reabsorption of magnesium have been made in most patients from measurements of creatinine clearance, nonprotein-bound serum magnesium and urinary excretion of magnesium. Increased parathyroid activity effected no alterations in tubular reabsorption of magnesium.

Effect of Carbohydrate Ingestion on Postprandial Lipemia

By *Margaret J. Albrink and Evelyn B. Man.* Department of Internal Medicine, Yale University School of Medicine, New Haven.

The serum lipids of 12 normal young men were estimated on 20 occasions before, and 3 hours after a breakfast containing 60 Gm. of fat, 42 Gm. of carbohydrate, and 22 Gm. of protein. The subjects had eaten nothing since supper at 6:00 the previous night. The serum neutral fat increased an average of 3.4 mEq./L. from the mean fasting level of 2.9 mEq./L. The magnitude of this rise varied from 1.5 to 5.5 mEq./L. The breakfast was repeated in 6 of the subjects who this time received a total of 120 Gm. of extra glucose as lemonade in 3 equally-divided doses given 1 hour before, ½ hour before, and again 1½ hours after the breakfast. There was no significant rise in serum neutral fat of any of the

subjects, the mean change being −0.2 mEq./L. 3 hours after breakfast. The lactescence which usually appears after this breakfast was barely discernible. In neither case were there consistent changes in the serum cholesterol or lipid phosphorus.

The results are taken to indicate that in the carbohydrate-fed subjects fat was more rapidly removed from the bloodstream than in those not receiving extra carbohydrate. Since the feeding of carbohydrate is known to favor the storage of fat, it appears that ingested fat destined to be stored is more rapidly removed from the bloodstream than fat destined to be burned. It is concluded that the status of carbohydrate metabolism in any individual is important in determining the magnitude of alimentary lipemia.

The Prevention of Hyperglycemia by Potassium Administration

By *Nancy Nichols*. Baker Clinic Research Laboratory and the Department of Medicine, Harvard Medical School, Boston.

It has been suggested by a number of workers that K is concerned with the metabolism of carbohydrate. Serum K levels fall in normals during glucose administration. The initiation of glucose utilization in diabetic acidosis is also accompanied by a lowering of serum K. Conversely, Kinsell, in 1953, was able to lower the blood sugar in steroid diabetes by the administration of large quantities of K.

We have studied the effect of a high carbohydrate meal with and without added K on blood sugar, serum K, muscle and liver glycogen, and the intracellular K content of muscle, liver and erythrocytes. Three groups of rats were studied: Group 1, rats fasted 48 hours; group 2, rats fasted 48 hours and given a pure carbohydrate meal during the next 24 hours; and group 3, rats fasted 48 hours and given a pure carbohydrate meal to which large quantities of K (0.5 mEq./Gm.) were added.

Blood sugars were as follows: group 1, 107 mg. % (87–113); group 2, 168 mg. % (155–175); group 3, 141 mg. % (135–145). The rats in group 3 retained an average of 2.8 mEq. K, or 15% of total body K. Serum K levels averaged 3.8 mEq. in group 1, 3.5 in group 2, and 4.3 in group 3.

Intracellular K values were: Muscle—group 1, 168 mEq./Kg. ICW; group 2, 162; group 3, 166; Liver—group 1, 181; group 2, 162; group 3, 170; RBC—group 1, 151; group 2, 142; group 3, 150. Muscle and liver glycogen levels were similar in the fed animals. Muscle—group 2, 0.75 Gm. %; group 3, 0.86; Liver—group 2, 7.94; group 3, 7.13.

It appears from this work that low levels of K in serum and cells cause hyperglycemia. Glycogen storage, however, is not decreased. Hence, the hypoglycemic effect of K must be related to a phase of carbohydrate metabolism other than glycogenesis.

The Effect of Insulin on the Blood Levels of Infused Pentoses in Man

By *James B. Wyngaarden, Stanton Segal and Joseph Foley*. National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

Ten to 20 Gm. quantities of d-xylose, d-arabinose, l-arabinose and d-lyxose have been infused intravenously into normal humans over 8 30-min. periods. When blood concentrations determined at various time intervals following infusion were plotted on semilogarithmic paper, straight lines were obtained. The biologic half-times of these sugars ranged from 44–96 min., and the urinary recoveries from 27–60%, in various subjects, no consistent differences being observed between pentoses. When the linear hemilogarithmic disappearance phase was established (45–60 min.) 0.1 μ of insulin/Kg. was injected intravenously. After a latent period of 10 min. a marked decrease of blood level of d-xylose and l-arabinose results, which is maximal in 30 min., and represents a change of 22–33% from the concentration obtained by extrapolation of the initial curve. After this period of change, a new linear hemilogarithmic disappearance curve is established whose slope is similar to that of the preinsulin curve. Insulin causes no such change in the disappearance curves of d-arabinose or d-lyxose. The effect of insulin of d-xylose and l-arabinose levels can be dissociated from the hypoglycemic effect, for glucose given intravenously following insulin did not alter the pentose response to insulin. Studies are in progress with other pentoses and hexoses designed to correlate stereochemical configuration of the sugars with insulin responsiveness, and to elucidate the mechanism of the reaction. The results of the studies conducted to date in man parallel those of Goldstein et al. in the eviscerated, nephrectomized dog, and suggest that insulin has affected the distribution of d-xylose and l-arabinose, but not of d-arabinose or d-lyxose, in body fluids.

A Quantitative Estimate of Net Splanchnic Ketone Production following Insulin Hypoglycemia in Man

By *Harry T. McPherson, Emile E. Werk, Jr., Frank L. Engel and Jack D. Myers*. Department of Medicine, Duke University School of Medicine, Durham.

Hypoglycemia is known to stimulate ketosis in normal and diabetic subjects. The present study presents data on the ketogenic response to insulin hypoglycemia in normal and cortisone-treated man, employing for the quantitative estimation of net splanchnic ketone production (NSKP) a previously described method which utilizes hepatic venous catheterization, and the measurement of estimated hepatic blood flow (EHBF) by the BSP method.

Mild hypoglycemia was induced in 6 essentially normal men, fasted overnight, by the intravenous injection of glucagon-free insulin (0.1 U/Kg.). Three hours later, the blood sugar levels having returned to normal, EHBF, NSKP, net splanchnic glucose production (NSGP) and oxygen consumption were determined before and after intravenous infusion of 500 ml. of 1.5% sodium octanoate, a known ketone body precursor. Compared to 16 normal subjects, the posthypoglycemic subjects showed no differences in blood sugar levels, EHBF, NSGP or oxygen consumption either before or after octanoate infusion. However, arterial and hepatic venous ketone levels and A-V differences were significantly increased after hypoglycemia, while NSKP was 160.7 ± 46.0 μM/min./M.^{2} compared to 34 ± 5.2 μM/min./M.^{2} in the controls. Both groups showed comparable increases in NSKP during octanoate infusion. Thus, insulin hypoglycemia leads to a significant increase in endogenous ketone body production without altering ketone production from octanoate.

Since cortisone suppresses fasting ketosis, 7 subjects were studied under conditions comparable to the above except for receiving 300 mg. cortisone acetate orally 2 hours before insulin. As in previous studies, cortisone significantly elevated EHBF and arterial blood glucose levels. The NSKP before and after octanoate in the cortisone-hypoglycemic group was slightly but not significantly lower than in the untreated hypoglycemic group. In both man and the rat cortisone has now been shown to suppress fasting ketosis but not to modify ketosis following insulin hypoglycemia.

The Inhibition of Insulin Action by Serum Gamma Globulin

By *Robert W. Weiger and Arthur R. Colwell*, Chicago

The insulin-inhibiting properties of a patient with hemochromatosis and labile insulin resistant diabetes were studied. This patient required up to 11,400 U insulin daily. ACTH therapy was associated with a transient disappearance of insulin resistance.

Insulin inhibition was tested in mice by the protective action of sera against convulsive and lethal doses of insulin. A close correlation was found between daily insulin requirement, blood sugar, and the insulin-inhibiting properties of the patient's sera. The insulin inhibitor varied directly with the level of gamma globulin in the patient's serum. The inhibitor was identified as a serum gamma globulin component by ammonium sulfate separation and by electrophoresis. The gamma globulin fraction of the patient's blood inhibited insulin action, as did whole serum.

I^{131}-labeled insulin mixed in vitro with the patient's sera was bound or retained in the gamma globulin zone on paper electrophoresis. A method was developed that measures as little as 0.00003 U of insulin. Normal serum and normal serum gamma globulin did not bind I^{131}-labeled insulin.

The gamma globulin fractions from the insulin resistant patient were capable of binding in vitro up to 35 times the amount of insulin bound by the gamma globulin fractions of nonresistant insulin-treated diabetics.

In vivo studies with I^{131}-labeled insulin in non-insulin-resistant patients who had received previous insulin therapy showed that insulin was bound in their gamma globulin fractions, in contrast to patients not given previous insulin therapy.

The results demonstrate the presence of an apparently abnormal gamma globulin moiety capable of producing a high degree of insulin inhibition in a patient clinically resistant to insulin therapy. The results also demonstrate a similar abnormal gamma globulin moiety, of less striking degree, in nonresistant diabetics who have received insulin therapy.

The Effects of Continuous Fructose Feeding in Diabetic Patients

By *John A. Moorhouse and Robert M. Kark*. Departments of Medicine, Presbyterian Hospital, Cook County Hospital, and University of Illinois Hospital, Chicago. (Aided by a grant from Mead Johnson and Company.)

Fructose restores metabolic activity in diabetic animal liver slices without insulin. This observation has been applied to the study of human diabetes. A well-balanced synthetic diet containing fructose was fed by intragastric tube and pump at a constant rate round the clock. The rationale of continuous feeding was to prevent the interprandial release of glucose from body stores. At suitable intervals glucose and fructose were interchanged, all other constitutents of the diet being kept constant. Pump feeding was given for up to 28 days. Measurements were made of glucose, fructose, acetone, pyruvate, lactate, sodium, potassium, phosphorus and nitrogen.

Studies have been completed on 8 patients with "pancreatic" diabetes and 1 healthy control. Insulin was stopped. When fructose feeding commenced, the blood glucose fell to the fasting level and glycosuria diminished or disappeared. In none of the patients was fructose found in the blood or urine. Blood and urine acetone levels fell markedly. Potassium and phosphorus were retained, indicating assimilation of carbohydrate. Nitrogen balance became positive. The extent of these effects was inversely proportional to the severity of the diabetes as measured by the fasting blood glucose level without insulin. Very severe cases were little affected. It is concluded: (1) The unitary theory of insulin action is correct for human diabetes. (2) Severe diabetes is characterized by an increased hepatic glucose release.

Similar studies are being carried out on patients with "steroid" diabetes. Preliminary results suggest

that the blood glucose levels are unaffected, despite which, blood acetone is lowered. It is concluded that the metabolic block in "steroid" diabetes differs from that in "pancreatic" diabetes.

Physiologic Action of a New Oral Hypoglycemic Agent

By *John A. Moorhouse and Robert M. Kark.* Departments of Medicine, Presbyterian Hospital, Cook County Hospital, and the University of Illinois Hospital, Chicago.

It has recently been demonstrated that certain sulfanilamide derivatives possess a blood glucose lowering effect in man. One of these, paratoluene sulfonylbutylurea (U-2043) has been used in metabolic studies in healthy subjects and patients with diabetes. In the fasting state single 3 Gm. doses produced sharp reductions in blood glucose levels which were maximal in 4 to 6 hours and lasted from 24 to 30 hours. The extent of the drop was from 50 to 200 mg. and, in general, varied directly with the height of the initial fasting glucose level. Hypoglycemic responses were marked in insulin-resistant and insulin-insensitive patients. It was surprising that the decrease in blood glucose produced no elevation in serum pyruvate or lactate levels. The drug was not effective in severe diabetic precoma. Prolonged metabolic balance studies, including measurements of glucose, pyruvate, lactate, acetone, cholesterol, sodium, potassium, phosphorus and nitrogen have been carried out. Maintenance of a continuous absorptive state by constant glucose tube-feeding completely abolished the hypoglycemic effect which had been observed in the fasting state. Continuous fructose tube-feeding permitted blood glucose to return to the fasting level and restored the hypoglycemic response. These findings suggest that the action of this drug is related to hepatic glucose release.

Relationship of Glucagon to the Mode of Action of Oral Antidiabetic Compounds

By *J. M. Tyberghein and R. H. Williams.* Department of Medicine, University of Washington, Seattle.

The introduction of sulfonylbutylurea and butyltolylsulfonylurea in the treatment of diabetes brings up the problem of their mode of action. It has been postulated, but not proved, that the oral antidiabetic compounds may act by decreasing glucagon production. Moreover, it has never been demonstrated that glucagon plays a role in the pathogenesis of diabetes. In order to study this point, attempts have been made to develop a technic for assaying glucagon in the serum. Such an assay would probably also permit one to determine whether oral antidiabetic compounds influence the production of glucagon.

In a previous study it was demonstrated that the liver-slice technic is a sensitive method for assaying glucagon. This technic has been applied in the present experiments, but in a preliminary study it has been shown that the serum itself cannot be used as incubation medium in the estimation of the glucagon activity of the serum. Indeed, since amylase, present in the serum, influences the glucose output markedly, it is necessary to remove it by using, essentially, Sutherland's procedure for the extraction of glucagon.

The glycogenolytic activity of such extracts was first extensively studied in rabbits. It was found that the extracts of portal vein serum had a glycogenolytic activity equal to 25 to 50% of the activity of an excess amount of glucagon. The extracts of aorta blood and vena cava blood had comparable glycogenolytic effect. Rabbits were treated with the aforementioned sulfonamides and the glycogenolytic activity of their serum was compared with untreated normal rabbits. Further studies were done in vitro to investigate the activity of those compounds on glycogenolysis in liver slices.

Investigations are also underway to compare the glycogenolytic activity of serum extracts from diabetic and nondiabetic persons.

The Adrenal Cortex and the Ketosis of Fasting and Insulin Hypoglycemia

By *Thomas T. Amatruda, Jr. and Frank L. Engel.* Department of Medicine, Duke University, Durham, North Carolina.

The demonstration that the ketosis of fasting or cold stress is suppressed in the cortisone pretreated rat, coupled with the enhancement of fasting ketonemia in adrenalectomized rats, suggested that the adrenal cortex exerts a restraining influence on ketosis. This problem was reinvestigated, utilizing insulin hypoglycemia as a ketogenic stimulus in 200-275 Gm. Vanderbilt strain male rats fed Purina Dog Chow. After a 24-hour fast, 0.5 U regular insulin was injected intraperitoneally, and blood sugar and ketone levels were measured at 0, 2, 4 and 6 hours. The 2-hour blood sugar was 16.8 ± 2.7 mg. % (mean ± s.e.) and the initial ketonemia of 5.84 ± 0.49 mg. % (as acetone) decreased to 2.85 ± 0.44 mg. % at 2 hours but rose to more than twice the fasting level at 4 and 6 hours. Pretreatment with 5 mg. of cortisone q. d. for 3 days confirmed the suppression of fasting ketosis (2.27 ± 0.17 mg. %). However, ketosis did occur at 4 and 6 hours after administration of 1.0 U of insulin, although the hypoglycemia at 2 hours (40.5 ± 2.4 mg. %) was less intense than in the controls.

The absolute increases in ketonemia did not differ significantly from the controls. When hypoglycemia comparable to that in control rats was induced with 1.5–2.75 U of insulin, ketonemia was

more pronounced, but still not different from the controls. Liver glycogen levels at 6 hours were 0.65 ± 0.17 Gm./100 Gm. liver in the cortisone pretreated insulin hypoglycemic rats, contrasted to 3.62 ± 0.41 in nonhypoglycemic cortisone pretreated rats. These results indicate that cortisone does not suppress the ketosis following insulin hypoglycemia.

In these studies, there appears to be an inverse relationship between development of ketosis and liver glycogen levels. The suppression of fasting ketosis by cortisone may be a reflection of the increased availability of endogenous carbohydrate rather than an indication of a direct effect of cortisone on ketosis.

The Effects of Cortisone on the Fructose and Glucose Tolerance Tests of Normal Men

By *Solomon Papper, Lawrence Saxon, Thaddeus E. Prout and Helen C. Alpert.* Medical Service and Research Laboratory, Boston V. A. Hospital and Departments of Medicine, Boston University School of Medicine and Tufts University School of Medicine, Boston.

A comparison was made of the effects of cortisone upon the glucose tolerance test with the influence of the steroid upon fructose tolerance. Each of 10 normal men was studied as follows. Control observations were made of the blood sugar levels following intravenous glucose on one occasion and intravenous fructose on another occasion. Subsequently, tolerance for each hexose was studied 4 hours after a single oral dose of 200 mg. cortisone acetate. In each instance, 50 Gm. of the hexose were administered intravenously in 20 minutes as 500 ml. of a 10% glucose or fructose solution.

Cortisone resulted in impaired glucose tolerance but did not affect the intravenous fructose tolerance. This selective action of cortisone on the metabolism of glucose suggests that one site of steroid action is prior to the splitting of 6 carbon molecules into 3 carbon fragments in the glycolytic cycle. Fructose infusion resulted in a definite rise in blood glucose concentration in 6 subjects. Urinary excretion of hexose after glucose administration was not significantly different from that following fructose.

Studies of the Relationship between Structure and Function of Steroids: The 2-Methyl-Corticosteroids

By *Grant W. Liddle, June E. Richard and Gordon M. Tomkins.* National Heart Institute and National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland.

The biologic properties of a new series of corticosteroid analogs, methylated at carbon #2, have been investigated in man, the dog, and enzyme systems from rat liver.

In steroids possessing an 11β-hydroxyl group (hydrocortisone, 9α-fluoro-hydrocortisone, and 11β-hydroxy-progesterone), the addition of the 2-methyl group greatly enhances sodium-retaining and potassium-losing activity. The most active member of this series, 2-methyl-9α-fluoro-hydrocortisone, is 3 times as potent as aldosterone and is, therefore, the most effective electrolyte-regulating steroid yet described. The eosinophil-depressing and ACTH-suppressing activities of 2-methyl-hydrocortisone and 2-methyl-9α-fluoro-hydrocortisone are slightly increased over those of the respective nonmethylated parent compounds.

By way of contrast, in steroids which do not possess an 11β-hydroxyl group (cortisone, for example) the addition of the 2-methyl group results in almost complete loss of biologic activity.

In man, 2-methyl-hydrocortisone appears to be metabolized in a distinctly different manner from hydrocortisone. Hydrocortisone disappears from the circulation with a half-life of about 2 hours, a major portion being converted to tetrahydrocortisone glucuronide, which is identifiable in large quantities in plasma and urine. 2-methyl-hydrocortisone, on the other hand, is removed from the circulation less rapidly than hydrocortisone, and 17,21-dihydroxy-20-ketosteroid glucuronides do not appear in significant quantities in plasma or urine following its administration.

Since studies in man suggest that 2-methyl-hydrocortisone is not metabolized to "tetrahydro" form, in vitro studies have been carried out using rat liver enzyme systems. 2-methyl-hydrocortisone has thus far been unique in that it is not reduced to "dihydro" or "tetrahydro" forms in these liver extracts, whereas all other corticosteroids tested, including other 2-methyl-corticosteroids, have been so reduced.

The specific nature of such enzymatic reactions is indicated by the fact that a purified extract can be obtained which will metabolize cortisone itself, but not cortisone analogs such as 2-methyl-cortisone, Δ^1 cortisone, or hydrocortisone.

Influence of Intravenous Adrenal Steroids on Sodium and Water Excretion in Normal Subjects

By *Joseph F. Dingman, John T. Finkenstaedt, John C. Laidlaw, Albert Renold, Dalton Jenkins, John P. Merrill and George W. Thorn.* Medical Service, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

The acute effects of intravenous hydrocortisone, corticosterone, aldosterone and prednisone on renal dynamics and sodium and water excretion were studied over 8 to 24-hour periods in 4 subjects. Five control and 9 hormone studies were performed. Clearance of inulin (C_{In}), PAH (C_{PAH}), osmols (C_{OSM}) and free water (C_{H_2O}), and the urinary ex-

cretion of Na, K, Cl, phosphate and uric acid were measured. Hydrocortisone (10 mg./hr.) produced a Na diuresis and an increase in C_{H_2O} initially, followed by Na and water retention. Prior administration of DCA prevented the initial Na diuresis. With simultaneous administration of intravenous Pitressin (15 mU/hr.) and hydrocortisone, the increased C_{H_2O} was not observed but the Na diuresis was unaltered. Corticosterone had effects similar to but less striking than hydrocortisone. Aldosterone (42 μg./hr.) in 1 subject induced Na retention out of proportion to water retention. In 1 subject, prednisone (2.5 mg./hr.) produced a striking Na and water diuresis which persisted for 8 hours. In another subject, marked water diuresis and slight Na diuresis occurred. The water diuresis was transiently inhibited by nicotine administration.

Since C_{In} was not elevated during the periods of natriuresis, an inhibition of tubular reabsorption of Na was implied. Although the tubular mechanisms responsible for this natriuresis have not been defined, inhibition of secretion or renal tubular action of endogenous salt-retaining corticoids may be postulated. Since there is ample evidence that adrenal steroids do not alter the antidiuretic action of administered Pitressin in human subjects, the diuretic effect of these steroids may best be ascribed to inhibition of ADH secretion from the neurohypophysis.

The Relationship of Acute Reduction in Blood Volume to the Release of "Aldosterone"

By *Daniel Fine, Leonard E. Meiselas and Theresa Auerbach.* Maimonides Hospital, Brooklyn, New York.

Physiologic studies have suggested that renal excretion of sodium is a function of the volume or dynamics of the extracellular compartment. We have studied the relationship of this function to aldosterone secretion during and following acute reductions of blood volume.

Phlebotomies of 8 cc./Kg. were performed on 2 active adults maintained on high sodium diets during test periods. Dietary, salivary, urinary and serum sodium and potassium, endogenous creatinine clearance, urinary 17-hydroxycorticoids and 17-ketosteroids were measured. Urinary aldosterone-like activity was assayed in adrenalectomized rats. Hemodilution and plasma expansion were calculated from hemoglobin and hematocrit changes.

Phlebotomy resulted in a marked rise in urinary "aldosterone" associated with a reduction of urinary sodium. Salivary sodium followed a similar pattern. Antinatriuresis persisted for 1 to 2 days and represented a 25–50% reduction in daily sodium excretion, but never resulted in urinary sodium below 90 mEq./day. Serum sodium and potassium, urinary potassium and creatinine clearance remained relatively constant. Sharp elevation of "aldosterone" excretion was not associated with significant alteration of other urinary steroids. Hemodilution was complete within 24-48 hours. However, restoration of blood volume in less than 2 hours, by withdrawal of fluid from the extravascular compartments produced by the infusion of salt-poor albumin, failed to prevent increased aldosterone excretion and antinatriuresis.

These studies suggest that acute reduction of blood volume, while not necessarily in itself the final stimulus, nevertheless initiates events culminating in sodium conservation, presumably mediated through a discreet adrenal response, i.e., increased aldosterone secretion. This mechanism does not depend upon potassium loading or increased serum potassium concentration, and is not necessarily associated with extremely low urinary sodium excretion.

Similar mechanisms, involving alteration of the volume or dynamics of extracellular fluid, may be responsible for increased aldosterone excretion reported in sodium deprivation, potassium loading, prolonged sweating and edematous states.

Metabolic Response to a Group Stress on a Metabolic Ward

By *William W. Schottstaedt, Ruth H. Pinsky, David Mackler and Stewart Wolf.* Department of Medicine, University of Oklahoma School of Medicine and the Oklahoma Medical Research Foundation, Oklahoma City.

Earlier studies established that significant alterations in fluid and electrolyte balance may occur in association with stressful life experiences despite carefully controlled dietary and water intake on a metabolic ward. The present pilot study focuses on the social and personal interactions of the ward community as a source of stressful stimuli. Data were gathered on the social structure of the community and the prevailing attitudes, values and taboos. Numerous significant deviations in metabolic balance were observed in association with problems arising on the ward. Several patients reacted in an almost uniform manner to the attitudes of the nursing staff concerning a series of psychologic tests which seemed to threaten one of their prime social values. The result was a subtle but widespread uneasiness among the whole group. During a period of 2 days before the problem could be resolved, 4 patients who were on metabolic balance studies showed marked deviations in their balance data. Sodium balance became markedly negative in all 4. In 3 of the 4, chloride, nitrogen and phosphorus balances also became negative. In these subjects the deviations could not be explained by food or fluid intake, exercise or medication.

Physical Activity: Attitudes and Performance in a Group of Obese Women

By *Ronald J. Dorris and Albert J. Stunkard.* Study

Program in Human Health and the Ecology of Man, Departments of Medicine and Psychiatry, New York Hospital-Cornell Medical Center, New York City.

The reciprocal effects of obesity and physical activity have received increasing attention in recent years. To investigate these relationships a group of 15 obese and 15 nonobese subjects were studied. The subjects were all women, carefully matched according to age, ethnic background and occupation. As an index of physical activity, each subject wore a calibrated pedometer for a period of 1 week. Their overt and covert attitudes toward activity were measured by means of a direct questionnaire and a sentence completion test devised for the purpose.

Preliminary results indicate that the obese women were less than half as active as their controls. The obese women walked 1.9 ± 1.6 miles per day as compared with 4.8 ± 2.2 miles per day for the control subjects. This difference is significant at the 1% level.

These values were in accord with the subjects' own estimates of their activities and their conscious attitudes; the obese women preferred sedentary activities and thought of themselves as inactive persons. Despite the differences in performance and self-image between the 2 groups, the spontaneous "urge to activity" appeared to be as great among the obese as among the nonobese subjects. This apparent discrepancy between motivation and performance may result solely from the added effort necessary for activity among obese persons. However, an additional explanation is suggested by the questionnaire studies. Thus, among obese subjects the usual response to depressive affects was passive acceptance and social withdrawal, in contrast to a greater tendency toward physical activity on the part of the nonobese controls.

Distribution and Physiologic Exchange of Mg^{28} in Animals and Man

By *H. N. Bane, A. S. Glicksman, M. K. Schwartz and J. J. Nickson.* Andre and Bella Meyer Physiology Laboratories of the Division of Experimental Surgery, and the Division of Physics and Biophysics and Medicine of the Sloan-Kettering Institute, Memorial Center, New York City.

The preparation of a new isotope of magnesium (Mg^{28}) with a half-life of 21.8 hours, a γ of 1.73 mev. and a β of 2.85 mev., has made possible an investigation of the distribution and physiologic exchange of intravenously administered Mg^{28}. The magnesium isotope with a specific activity varying from 1.73 to 6.18 $\times 10^5$ cpm/mEq. was administered, and samples of tissues, blood and urine were taken at intervals for 24 hours. The radioactivity was determined by counting the γ emission with a scintillation counter, and the chemical magnesium was determined by the titan yellow method.

The distribution of Mg^{28} in various tissues was studied in rats killed at 2, 4, 12 and 24 hours. By counting samples of muscle, skin, bone and individual internal organs, it was possible to account for 85 to 95% of the injected radioactivity. Calculation of the differential absorptive ratios (DAR) revealed almost uniform distribution at the end of 24 hours. The "safe dose" was found to be 2.76 μc./Kg. body weight.

Physiologic exchange and excretion of intravenously administered Mg^{28} was studied in 6 dogs and 4 patients. In the dogs, 69.6%, and in the patients an average of 82% of the administered dose was retained. Data pertinent to the blood fall-off curve, cumulative excretion of the isotope, and calculation of the "magnesium space" and exchangeable magnesium were obtained.

The data indicate that the volume of distribution of Mg^{28} is larger than the extracellular fluid. However, the total exchangeable magnesium was found to be approximately 40% of the theoretic intracellular magnesium. This would indicate that during the time of experimental observation a large quantity of magnesium does not enter into the "metabolic pool" and appears to be "fixed."

The Effect in Humans of Alterations of Extracellular pH on the Serum Potassium Concentration

By *Belding H. Scribner, Mario Villamil, Ben T. Uyeno and James M. Burnell.* V. A. Hospital and the Department of Medicine, University of Washington School of Medicine, Seattle.

The authors' observation in dogs that acidosis increases, and alkalosis decreases, the serum potassium concentration independently of changes in total body potassium resulted in the hypothesis that the relationship between extracellular and intracellular potassium can be altered by a change in extracellular pH. The present study confirms this hypothesis in 10 human experiments.

During the period of pH change, an attempt was made to alter potassium balance in the direction opposite to the expected change in the serum concentration. Glycogen stores were changed as little as possible.

A typical case study is a patient with acute ethylene glycol poisoning. This patient had an initial plasma pH of 7.02 (38°C.) and an initial serum potassium concentration of 6.8 mEq./L. Eighteen hours later, after receiving intravenous sodium bicarbonate and potassium chloride, his plasma pH was 7.51 and his serum potassium concentration was 4.4 mEq./L. During this period his potassium balance, corrected for nitrogen, was +39 mEq., and his intracellular potassium (calculated from potassium balance and chloride space) increased 30 mEq.

In 4 acidotic and 6 alkalotic patients extracellular pH change invariably resulted in an opposite change in the serum potassium concentration. For every 0.1 U change in pH there was a 0.4 to 1.5 mEq./L. change in the serum potassium concentration. The mean change was 0.7 mEq./L. The pH effect was greater when the initial serum potassium concentration was elevated.

These interrelationships have important clinical implications: (1) The serum potassium concentration will reflect more accurately the total body potassium if the effect of pH change is considered. (2) Other factors, such as dehydration and adrenal steroids, which have been considered causes of change of the serum potassium concentration must be restudied with attention directed to maintenance of constant extracellular pH. (3) In the management of acute renal failure, prevention of acidosis and production of alkalosis will lower the serum potassium concentration and will protect against potassium intoxication.

Metabolic Effects and Plasma and Renal Clearances of Intravenously Administered Diamox in Man

By *Alvin Essig, Marian C. Isaacs, Jacob Grossman and Raymond E. Weston.* Montefiore Hospital, New York City. (Aided by grants from the National Heart Institute, New York Heart Association and the National Foundation for Infantile Paralysis.)

Despite widespread clinical use of Diamox (2 - acetylamino - 1,3,4 - thiadiazole - 5 - sulfonamide), few comprehensive studies on the metabolic effects and plasma and renal clearances of this carbonic anhydrase inhibitor in normal human subjects or nonedematous cardiac patients are available. Therefore, the response to single intravenous injections of 5 to 10 mg./Kg. of Diamox were studied in 1 normal and 1 mildly hyperthyroid subject, and in 2 patients with rheumatic heart disease and minimal cardiac failure, maintained on fixed fluid and 15 mEq. sodium intakes. Supplementary NaCl was given to 2 patients, and organic potassium salts were given to 2 others.

Metabolic balances for electrolytes and water, urinary pH and excretion of ammonia, titratable acidity and bicarbonate, and the corresponding blood chemistries were followed.

In every patient Diamox produced significantly increased urinary pH and excretion of bicarbonate, sodium, potassium and water, with decrease in titratable acidity and ammonia. These effects were maximal during the first and second hours, with progressive return toward control levels during the second to sixth, and sixth to 12th hours. Urinary titratable acid and ammonia during the 12th to 18th and 18th to 24th hours slightly exceeded control values. Calculated base deficit (urinary titratable acid plus ammonia minus bicarbonate) after 24 hours ranged from 1.2 to 2.4 mEq./Kg. On the following days, urinary titratable acidity and ammonia increased moderately, with an equivalent decrease in fixed base excretion. However, complete compensation for the acidosis required 3 to 7 days. One subject on a 170 mEq. NaCl intake, when given Diamox at 48-hour intervals, before correction of the acidosis, exhibited diminished responses despite doubling of dosage.

Within six hours, 75–83% of the 5 mg./Kg. dose was excreted in the urine, and plasma concentrations fell to 3–12% of the 5 to 10-minute values. Subsequently, although plasma levels were very low, the relatively low titratable acidity and ammonia excretion, despite hyperchloremic acidosis, suggested persistence of Diamox effect.

On the Mechanism of Rubidium-Induced Acidosis

By *Anne T. Lambie, Arlene M. Roy, Arnold S. Relman, Belton A. Burrows and William B. Schwartz.* Departments of Medicine, Boston University School of Medicine and Tufts University School of Medicine, Boston.

In the nephrectomized rat, rubidium chloride (RbCl) repairs K-deficiency alkalosis as efficiently as does KCl. This probably results from displacement of intracellular hydrogen by administered cation. In the intact rat, RbCl produces metabolic acidosis, whereas equivalent doses of KCl do not. The present study attempts to elucidate the role of tissue and renal exchanges of electrolytes in the pathogenesis of rubidium-induced acidosis.

Three hundred Gm. rats were tube-fed a standard diet for 2 days and then divided into 2 groups. For the next 2 days, group 1 received the diet plus 20 mEq./Kg./day of KCl; group 2 received the diet plus equal amounts of RbCl. Final serum values in group 1 were: CO_2 content, 23.9 ± 1.3 mEq./L.; K, 3.86 ± 0.58 mEq./L.; in group 2: CO_2 content, 13.2 ± 4.8 mEq./L.; K, 2.58 ± 0.84 mEq./L.; Rb, 1.28 ± 0.24 mEq./L. The final potassium and sodium balances in group 1 were essentially zero. The group 2 rats retained 8.74 ± 0.94 mEq. of rubidium (approximately 70% of the load) and simultaneously lost 8.36 ± 1.9 mEq. of potassium and 1.41 ± 0.34 mEq. of sodium. Changes in urine pH, titratable acid and bicarbonate were negligibly small. Total ammonium excretion during loading remained unchanged in group 1, but fell by 1.0 mEq. in group 2 ($p < .01$).

Balance data (confirmed by muscle analyses) indicate that half the intracellular potassium was replaced by rubidium. Displacement of tissue hydrogen may have contributed to the acidosis, but renal retention of acid consequent to reduced ammonium excretion could of itself account for the lowered extracellular bicarbonate. Thus, the kidneys not only failed to respond in the expected manner to this severe acidosis, but contributed significantly to

its development. The mechanism by which rubidium inhibits ammonium excretion remains to be elucidated.

Organic Acid Excretion in Alkalosis

By *Morris A. Lipton and Shirley K. Carroll.* Investigative Medicine Service, V. A. Hospital and the Department of Medicine, Northwestern University Medical School, Chicago.

Animals made alkalotic by the ingestion of large quantities of sodium bicarbonate excrete citric acid in quantities 10 to 50 times above that of normals. Similar rises occur in the excretion of other organic acids.

Experiments have been performed to further elucidate the mechanism by which these urinary changes occur. (1) The urine of rats maintained on a low chloride diet contains large quantities of citric acid, suggesting that this acid is synthesized to spare chloride, while neutralizing cations. Further evidence for this view is obtained from acute experiments in which sodium bicarbonate is given intravenously to dogs. In such studies, urinary citric acid rises 50-fold in about 5 hours and begins to exceed chloride excretion. (2) When a carbonic anhydrase inhibitor (Diamox) is administered to animals made alkalotic by sodium bicarbonate ingestion, citric acid excretion falls precipitously, even though the urine becomes more alkaline. That this is due to the conversion of alkalosis to a systemic acid is shown by direct measurements of blood pH, and by the demonstration that if alkalosis is maintained in the Diamox-treated animal by the continuous administration of bicarbonate intravenously, the excretion of citric acid remains elevated.

Experiments are in progress to determine the role of potassium and the site of origin of the citric acid excreted. Since citric acid represents less than 50% of the total organic acids excreted, chromatographic studies are in progress to study the alterations in these compounds in alkalosis.

The Relationship between Plasma Osmolality and Concentration in Disease States

By *Albert L. Rubin, Warren S. Braveman, Richard L. Dexter, Parker Vanamee and Kathleen E. Roberts.* Department of Medicine, Cornell University Medical College, Second (Cornell) Medical Division, Bellevue Hospital, and Sloan-Kettering Institute, New York City.

In healthy persons, the total osmolality of the plasma is held to be largely determined by the sum of electrolyte concentrations, and is regarded as one of the most stable features of the *milieu intérieur*. In normal subjects, the mean total osmolality by the method of freezing point depression is 280 ± 10 mOsm./Kg. H_2O.

In 250 patients with various disease states including a variety of acid-base disturbances, we performed 550 direct measurements of total osmolality, and compared this value with the osmolality calculated from the levels of known plasma electrolytes. Measured total osmolality ranged from 220 to 475 mOsm./Kg. H_2O. In 172 patients, this value, though often abnormal, was equal to the calculated osmolality; all of these patients recovered. In 78 patients the measured osmolality exceeded by 40–125 mOsm./Kg. H_2O the calculated value, and the difference could not be accounted for by urea nitrogen, glucose, protein or other commonly measured plasma constituents. This phenomenon was observed in a variety of clinical conditions, including uremia, metastatic cancer, lymphoma, liver cell necrosis, myocardial infarction, and overwhelming infections. Ninety-eight % of this latter group died within 2 weeks after the finding of hyperosmolality.

These findings indicate the presence, in the plasma of critically ill patients, of one or several osmotically active substances not included among the electrolytes or other commonly measured constituents of the plasma. So far, efforts to identify these substances have been without avail. The finding of unaccountable hyperosmolality would appear, nevertheless, to be of ominous prognostic significance.

Studies in Cholesterol Degradation

By *Marvin D. Siperstein.* Department of Internal Medicine, the University of Texas Southwestern Medical School, Dallas.

To elucidate the regulatory mechanisms of cholesterol metabolism, studies were undertaken to delineate factors involved in cholesterol breakdown. In experimental animals, as well as man, most of the body cholesterol is converted to conjugated bile acids in the process of its elimination. The purpose of the present study was to characterize the following features involving the formation of this key intermediate in cholesterol catabolism: (1) the tissue and intracellular sites of conjugation, (2) the intermediate compounds formed in the metabolic pathway, (3) the mechanism and cofactor requirements of the reaction.

Studies were conducted primarily with guinea pigs and rats, using tissue slices and cell-free systems from kidney, brain, intestine, spleen and liver.

The reaction in a whole homogenate required the presence of adenosine triphosphate and coenzyme A, as well as the bile acid and taurine. Further purification of the system allowed a separation of the reaction into 2 steps. Examination of the first step has led to the discovery of an activation reaction of bile acids involving the formation of bile acid-coenzyme A derivatives, e.g., cholyl-CoA. This process can be carried out only by the microsomes of liver. A second reaction, catalyzed by an enzyme located in the supernatant of liver, results in the formation of the amide bond between the activated bile acid and

taurine, to produce the conjugated bile acid, e.g., taurocholic acid.

On the basis of these findings, it is concluded: (1) Bile acids are conjugated exclusively in the liver. (2) The reaction proceeds in 2 steps, an activation reaction carried on in the microsomes to form a bile acid-CoA derivative, followed by a conjugation reaction performed in the supernatant fraction. (3) ATP is a required cofactor for the first step.

Cholyl-CoA has been isolated and purified, and represents the first demonstration of the presence of activated sterols in nature.

Studies in Carotenemia

By *John F. Kachmar and Abraham M. Frumin.* Department of Laboratories, Albert Einstein Medical Center, Southern Division, and the Department of Medicine, Sidney Hillman Medical Center, Philadelphia.

A patient with carotenemia due to the ingestion of 2 lb. of carrots daily for 3 months was found to have a serum carotene of 1000 μg. %. The stools showed a marked increase in carotene, but none was found in the saliva, sweat, tears or urine. Carotene determinations over a 2-month period showed a logarithmic decline in serum levels. The cause for the development of carotenemia and the relationship of this logarithmic curve to the disappearance of carotene from the serum was considered. Heparin was administered intramuscularly to this patient, and normal patients, in an attempt to release carotene into the peripheral circulation. The results obtained indicate that, in sporadic instances, heparin will increase serum carotene within a 2-hour period.

GASTROINTESTINAL SYSTEM

Intraluminal Pressures at the Esophagogastric Junction in Healthy Persons and in Patients with Cardiospasm (Achalasia of the Cardia)

By *Brian Creamer, F. Earl Fyke, Jr., Charles F. Code and Arthur M. Olsen.* Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The intraluminal pressures at rest and during deglutition were measured at the esophagogastric junction to define the pattern in health and to explore the abnormality in cardiospasm. The pressures were measured by withdrawal of a miniature, electromagnetic pressure transducer or an open-tip tube connected to a manometer through the junctional area from stomach to esophagus.

A zone of high-resting pressure, 2 to 3 cm. in length, interposed between the stomach and esophagus, has been found regularly in healthy persons. The high-resting pressure in this junctional region decreases after a swallow, and rises later with the arrival of the peristaltic contraction.

In patients with cardiospasm the resting pressure at the junctional region was found to be of normal dimensions; no excessive pressure could be demonstrated. A decrease in pressure in this region on swallowing usually was absent, and the contraction was recorded earlier than in healthy persons. When cardiospasm is present the obstruction after swallowing is therefore due to failure of relaxation of the esophagogastric junction.

Effect of Chlorpromazine on Gastric Secretion in Dog and Man

By *David C. Sun and Harry Shay.* Fels Research Institute, Temple University School of Medicine, Philadelphia.

To obtain information on the mechanism of action of chlorpromazine on gastric secretion, studies were done in dogs to determine its effect on gastric secretion induced by sham feedings, intermittent mecholyl injections and intermittent histamine injections.

In 2 dogs, each with esophgotomy and a gastric fistula, volume of secretion, acid and pepsin output after sham feeding were markedly inhibited by chlorpromazine in the doses used. The degree of produced inhibition increased as the dose of drug increased. Since the vagi provide the sole pathway for the gastric secretory impulses originating in the brain in sham feeding, we were interested to determine whether chlorpromazine exerts its inhibitory action centrally or peripherally. Studies were conducted with intermittent mecholyl injections on 2 dogs, each with a Heidenhain pouch. Chlorpromazine produced no inhibition of pepsin output and had only a slight inhibitory effect on acid output. The results of these experiments would make the main inhibitory action on gastric secretion in the dog a central rather than a peripheral parasympatholytic effect.

In man, chlorpromazine was found to inhibit both basal gastric secretion and the adrenal phase of secretion induced by insulin hypoglycemia. Elorine sulfate used with chlorpromazine produced an interesting inhibitory effect on gastric secretion. Efforts are being made to determine whether this is merely an additive effect, or possibly potentiation or synergism. With the doses used, no undesirable side effects were observed.

The Influence of Various Agents upon the Duodenal Response to Apomorphine in Man

By *Herman Steinberg, Edward B. Babcock, Lawrence C. Rosenberg, Marvin H. Sleisenger and Thomas P. Almy.* Second (Cornell) Medical Division, Bellevue Hospital, New York City, and the Department of Medicine, Cornell University Medical College, New York City.

Spasm of the second and third portions of the duodenum has been shown to be part of the efferent mechanism in nausea and vomiting. This provides an objective indicator of the action of emetic and antiemetic agents.

In the present study, motility of the human duodenum was recorded by a balloon-kymograph technic. The duodenal response to a centrally-acting emetic stimulus (apomorphine) was observed and compared with the effect of the drug following premedication with chlorpromazine, methantheline, dimenhydrinate, Amytal and locally applied procaine and pontocaine. Of the 33 patients studied, all were free of gastrointestinal and neurologic disease, except 1 decerebrate and 1 who had suffered a cord transection at T_1.

The subcutaneous administration of 1.5 to 2.5 mg. of apomorphine regularly produced nausea with or without mild to violent retching. Nausea was invariably preceded by increased tonus of the duodenum. When smaller doses were employed, increase in duodenal tonus occurred without associated nausea.

These effects of apomorphine could not be consistently inhibited by methantheline (9 subjects), dimenhydrinate (3 subjects), Amytal (4 subjects), or local anesthesia (7 subjects). Chlorpromazine, however, succeeded in regularly preventing duodenal spasm due to apomorphine (10 subjects).

These results indicate that duodenal spasm during nausea and vomiting is much more powerfully inhibited by a centrally-acting than by a peripherally-acting agent. This permits comparison of the pharmacologic action upon the duodenum of chlorpromazine and anticholinergic drugs, and provides an objective method for the evaluation of antiemetic drugs in man.

Adrenocortical Hyperactivity in Peptic Ulcer as determined by Plasma and Urinary 17-Hydroxycorticosteroid Levels

By *Jayme Rozenbojm, Lewis J. Krakauer and Seymour J. Gray.* Department of Medicine, Harvard Medical School and the Peter Bent Brigham Hospital, Boston.

Previous studies on gastric secretion in man and in experimental animals have suggested that the stomach is capable of adrenocortical stimulation independent of the vagus nerve and gastric antrum. An adrenal-gastric relationship has been further suggested by correlative statistic studies of adrenal and gastric function.

Pain, peptic ulcer *de novo*, and reactivation of quiescent ulcer have been observed following administration of ACTH or cortisone. Nevertheless, there have been conflicting reports concerning the elevation of the urinary adrenal corticoids in peptic ulcer. The direct demonstration of adrenal hyperactivity paralleling gastric hypersecretion has not been documented heretofore.

Improved technics for determining plasma-free and total 17-hydroxycorticosteroids now provide reliable indices of adrenocortical function. The present study evaluates adrenal activity by application of these methods before and after intramuscular ACTH stimulation in 9 normal subjects, in 8 patients with gastric ulcer and in 8 duodenal ulcer patients, with a concomitant study of urinary steroid excretion.

Significantly increased levels of plasma-free 17-hydroxycorticosteroids were observed in gastric and duodenal ulcer. The plasma total 17-hydroxycorticosteroids were significantly elevated in the duodenal ulcer group alone, with a parallel elevation of the 24-hour urinary 17-hydroxycorticoids.

Characteristic elevation of both the free and total plasma 17-hydroxycorticosteroids were noted in each group following intramuscular ACTH administration. The duodenal ulcer group alone, however, demonstrated a percentage increase significantly above normal, suggesting increased adrenocortical responsiveness.

The data afford further corroborative evidence for an adrenal-gastric relationship.

Plasma 17-Hydroxycorticoids in Peptic Ulcer Disease

By *Alvin J. Cummins, Harmon E. Keyes and Marie H. Jones.* Gastrointestinal Laboratory, Department of Medicine, University of Tennessee Medical Units, and the John Gaston Hospital, Memphis. (Aided by grants from Lakeside Laboratories and Smith, Kline and French.)

Despite considerable evidence linking the administration of adrenal steroid hormones to increased gastric secretion and exacerbation of peptic ulcers, and the intimation that adrenal dysfunction may be concerned in the etiology of ulcer, there have been surprisingly few studies of adrenocortical function in human peptic ulcer disease. In the present experiments plasma concentrations of 17-hydroxycorticoids were compared in a group of 10 roentgenologically proven ulcer patients (9 duodenal, 1 gastric) with those in 8 nonulcer control subjects. All venous blood samples were drawn under identical conditions at approximately the same time of day. None of the patients had clinical evidence of endocrine disorder. The mean plasma concentration of the ulcer patients was 13.9 $\gamma\%$ (range, 8–21) and that of the control subjects was 14.8 $\gamma\%$ (range, 11–19).

Following taking of the blood sample, 8 of the ulcer subjects and all 8 control patients received an intravenous infusion of 500 cc. of 5% glucose, to which 25 U of ACTH was added. The infusion was given at a constant rate over a 4-hour period. Blood samples for steroid determination were again drawn immediately following the termination of the infusion. The postinfusion concentration of 17-hydroxycorticoids in the ulcer patients was 41.8 γ% (range, 30–58) and in the control subjects 40.6 γ % (range, 28–51). Eosinophil counts performed before and after the infusion showed a mean fall of 51% in the ulcer group and 46% in the controls.

It is concluded that by these assays of function no detectable alteration in adrenocortical activity can be demonstrated in the patient with active peptic ulcer disease. Basal levels of plasma hormones are not significantly different, and the responsiveness to adrenal stimulation appears unaltered. While this type of study fails to provide a definitive answer to the question of the relationship of the adrenal cortex to the genesis of ulcer, it offers no support to the concept of adrenal overactivity in human peptic ulcer.

Secretion of Electrolytes by the Human Pancreas

By *David A. Dreiling and Henry D. Janowitz.* Departments of Medicine and Surgery, The Mount Sinai Hospital, New York City.

The pattern of electrolyte secretion of the human pancreas was studied in 59 normal subjects during secretin stimulation and following carbonic anhydrase inhibition by Diamox. Pancreatic juice was collected by duodenal intubation without gastric contamination. Following intravenous secretin, the concentration of Na was similar to that of the plasma (139–143 mEq./L.); K was elevated above plasma levels (6–9 mEq./L.); the concentrations of both were relatively constant, and independent of the rate of secretion. Bicarbonate (36–140 mEq./L.) varied directly with the rate of flow, Cl (120–17 mEq./L.) varied inversely with HCO_3, with "total" anion concentration (HCO_3 + Cl) remaining remarkably constant (155–157 mEq./L.) and approaching the osmolarity of the plasma. In 14 subjects, the sodium salt of Diamox, in doses of 80 mg./Kg. and higher, caused a marked inhibition of volume flow and output of HCO_3, independent of alterations in plasma electrolytes. The concentrations of Na and K of the juice were unchanged, as well as the reciprocal relations between Cl and HCO_3.

The pancreas thus tends to secrete an isotonic fluid despite variations in rate of flow; and the formation of HCO_3 appears to be under the catalytic influence of carbonic anhydrase. In chronic pancreatitis (19 cases) the flow–bicarbonate relationship was disturbed, with normal rates of secretion of H_2O and impaired bicarbonate secretion.

Comparative Value of Serum and Urinary Amylase in the Diagnosis of Acute Pancreatitis

By *E. I. Saxon, W. C. Hinckley, W. C. Vogel and L. Zieve.* Departments of Medicine and Surgery and Radioisotope Service, V.A. Hospital and University of Minnesota, Minneapolis.

Simultaneous determinations of serum concentration and quantity excreted in the urine per hour were performed serially in 22 patients with acute pancreatitis without renal insufficiency. The urinary excretion rate was always abnormal when the serum concentration was abnormal, and the relative degree of abnormality of the urine values was greater. In every patient the urinary excretion was abnormal one or more times when a simultaneous serum value was normal. The urine value was abnormal 83 times when the serum concentration was normal. In no instance was the serum concentration abnormal when the urine was normal. The serum concentration usually dropped within normal limits by the second to third day of the illness. However, the urinary excretion per hour generally remained abnormal 7–10 days longer. In 1 patient with a pancreatic cyst containing approximately 25,000 U % amylase the daily urine excretion remained abnormal 6 weeks after the serum concentration had returned to normal. For clinical purposes, 2-hour collections of urine are as effective as 24-hour collections.

Effect of a Hypertonic Solution on Intestinal Absorption

By *Thomas R. Hendrix.* Evans Memorial and Massachusetts Memorial Hospitals, Boston

Absorption has been studied in normal human subjects by perfusing jejunal segments through intestinal tubes. In such technics, as generally used, incomplete recovery of the test solution introduces an immeasurable error. To permit calculation of such loss, sulfobromophthalein was added to the test solution and absorption calculated:

$$\text{amt. absorbed} = \text{amt. infused} - \frac{\text{BSP infused}}{\text{BSP recovered}} (\text{amt. recovered})$$

BSP is soluble, easily measured and, though slightly absorbed, as much as 97.5% can be recovered from perfusates.

Two hundred ml. of test solution containing 100 mg. BSP and 10 μc. I^{131} in isotonic NaCl or 25% glucose was infused into the jejunum 25 cm. above the aspirating orifices. Intestinal contents arriving at the distal orifices were constantly aspirated for 90 to 120 minutes.

In 44 experiments BSP recovery was 69.9% ± 22.4. The variability of BSP recovery emphasizes the error which may affect intestinal absorption studies by intubation technics.

In 15 studies, I^{131} absorption from isotonic saline was 36.3% ± 12.6 of the amount introduced. Net absorption of fluid was 20 ml. In 5 experiments with 25% glucose, I^{131} absorption decreased to 6.1% ± 5.9. Glucose was absorbed more rapidly than iodide. Two hundred and fifty to 600 ml. of fluid were secreted.

Others have postulated, on indirect evidence, that the dumping syndrome is caused by rapid fluid shifts into the intestine. Our direct evidence shows that considerable fluid transfer in response to hypertonic solutions is possible—as much as 300 ml. in 20 minutes in a 25 cm. segment. In our supine normal subjects, pulse rate rose by an average of 14, and systolic blood pressure by 12 mm. Hg. Hematocrits were unchanged, as was the plasma volume on 1 determination.

Blood Carotene and Steatorrhea

By *Julius Wenger*. Department of Medicine, Frank Billings Medical Clinic, University of Chicago, Chicago.

The concentration of carotene in blood has been used as an estimate of fat absorption by investigators interested in small bowel disease. The strikingly low values noted in sprue suggest that in chronic steatorrhea the depletion of body stores of this fat-soluble vitamin occurs regularly. The present study attempts to relate the plasma concentration of carotene to the 24-hour excretion of fat in the stools in a series of 60 patients studied in a 1-year period. Nine patients were thought to have the classic "sprue syndrome"; decreased excretion of fat in the stools, and a rise in plasma carotene generally paralleled their clinical improvement. In 24 additional patients, other types of gastrointestinal disease producing steatorrhea were associated with low concentrations of plasma carotene.

In 24 patients without demonstrable disease, the excretion of fat and the blood carotene were normal. A few exceptions to this pattern were noted in a group of patients who had a normal fat excretion but a borderline low carotene level, presumably due to inadequate intake of carotene in food prior to the test. The clinical implications of blood carotene determination as a screening test for steatorrhea and its usefulness as a simple test to follow the course of certain disorders of fat absorption are evident.

INFECTIOUS DISEASES

The Effects of Housing on the Incidence and Spread of Common Respiratory Diseases among Air Force Recruits

By *Stanley H. Bernstein and William F. Taylor*. Division of Preventive Medicine, U. S. Air Force, with the financial support of the School of Aviation Medicine, USAF.

The purpose of this study was to determine the relative merits of 2 specific types of barracks housing Air Force recruits with respect to the spread of streptococcal infections, influenza and ARD (acute respiratory disease, undifferentiated).

Two large groups of recruits were studied from November 1952 to June 1953 at a large Air Force Base in the northeastern United States. While these 2 groups were exposed to nearly identical training, eating and medical care conditions, 1 group was housed in large dormitory-style barracks, the other group in barracks with partitioned rooms which slept a maximum of 6 men in each. No other differences between the 2 groups could be detected which might bias the comparison.

Bacteriologic and serologic studies were done on all recruits hospitalized with a febrile respiratory illness. The rates obtained for each of the specific diseases studied were analyzed, taking into account the simultaneous variation of calendar month and "seasoning" of the population.

The presence of a strong seasonal factor in the incidence of the respiratory diseases was apparent. Susceptibility to the diseases, except possibly for influenza, also depended upon the length of exposure of each man to the environment. With respect to the transmissibility of each disease studied, correlation analysis was carried out to compare the 2 barracks types.

The data indicate that the transmission of ARD was not associated with a difference in barrack types. The spread of an epidemic of influenza A-prime appeared more rapid in the open-bay barracks. The risk of transmissibility of streptococcal infections was greater in the closed-bay barracks, although the incidence rate was somewhat lower than in open-bay barracks. The secondary attack rate was high for streptococcal disease, low for ARD. This suggests that individuals, treated effectively for streptococcal illness, may not develop type-specific antibodies to the epidemic streptococcal type and are more susceptible to reinfection with the same strain. The low reinfection rates for ARD suggest partial immune mechanisms.

Zone Electrophoresis and Poliomyelitis

By *Anwar A. Hakim and Milton S. Saslaw*. Department of Medical Research, National Children's Cardiac Hospital, Miami, Florida.

Zone electrophoresis can be used to demonstrate antigen-antibody reactions in poliomyelitis. Human

sera from 3 normal healthy individuals and from 4 patients convalescing from poliomyelitis were studied for antibody content. Commercially available poliomyelitis vaccine provided the antigen.

The antigen-antibody reaction was carried out in 2 ways. (1) Accurately measured volumes of vaccine and serum were placed on the filter paper of a previously equilibrated electrophoresis apparatus. After 4 hours interaction, a current of 200 volts, 8 ma., was applied for 18 hours. The filter paper was dried and stained for protein. (2) A mixture of 1 volume of serum, 15 volumes of vaccine, and 2 of buffer was allowed to stand in the refrigerator for 19 hours, followed by 1 hour at room temperature. This mixture was applied to the filter paper which then was treated as above. Two types of electrophoresis apparatus were employed, as well as different buffers.

Spectrophotometric examination at 590 mμ wave length confirmed the presence of antigen-antibody complex in all convalescent and 2 healthy individuals. Approximate quantitation revealed the patient with the weakest reaction showed twice the intensity of the strongest healthy serum.

By this technic, we anticipate similar antigen-antibody reactions in other diseases from which known antigens have been isolated (bacterial, viral, rickettsial, etc.). With sera of high titer of known antibodies, recognition of unknown infecting antigens is possible.

This procedure may be calibrated against sera of known titers, and then utilized for quantitative titration of either antigens or antibodies.

Klebsiella in Pulmonary Disease

By *William Weiss, George M. Eisenberg, Alfred Spivack, Harold Kayser, Jay Nadel and Harrison F. Flippin.* Philadelphia General Hospital, Philadelphia.

Clinically, few known bacteriologic studies indicate that *Klebsiella* species and *Aerobacter aerogenes* are indistinguishable, and justify the inclusion of these organisms into a single group, *Klebsiella*. Individual strains within the group may be differentiated on the basis of capsular types, 77 having been demonstrated to date. With this knowledge, and sera for differentiating types 1 to 10, a study of the relationship between *Klebsiella* species and pulmonary disease has been carried on for the past 4 years at the Philadelphia General Hospital.

The nosocomial prevalence of *Klebsiella* at this institution varies from 2% in the pharyngeal secretions of employees to 13.7% in the sputum of patients with all kinds of respiratory disease. Patients without obvious respiratory disease have these organisms in pharyngeal secretions in 8.2% of cases.

The majority of respiratory strains of *Klebsiella* species cannot be typed with sera for types 1–10. Of the 22.5% which can be typed, the most common strain is type 2 (8%) with smaller numbers of types 1, 4, 7, 8 and 9.

The kind of pulmonary disease most often associated with *Klebsiella* in the sputum is pneumonia. Types 1, 2 and 4 are more often associated with destructive lung disease (abscess and atelectasis) than are the higher types. In fact, the latter are sometimes found in patients without respiratory disease, whereas the former are not.

The antibiotic susceptibilities of 188 respiratory strains show that 81% are inhibited by Chloramphenicol, 74% by streptomycin and 63% by tetracycline. The susceptibilities of 26 strains of types 1, 2 and 4 are similar.

Approximately half of the *Klebsiella* strains isolated from patients who are not on penicillin therapy are types 1, 2 and 4, whereas almost all strains isolated from patients on penicillin therapy are of the higher types. The relationship between capsular type and penicillin therapy requires further investigation to elucidate the mechanism involved.

"Endotoxic" Effects Produced in Man by a Purified Bacterial Lipopolysaccharide

By *Jay P. Sanford and Maurice Landy.* Divisions of Surgery and Immunology, Walter Reed Army Institute of Research, Washington, D. C.

The role of endotoxins (pyrogens) liberated from Gram-negative bacteria in the pathogenesis of many infectious processes, shock and fever itself has not been well defined. The endotoxic properties of a highly purified, immunologically characterized bacterial lipopolysaccharide derived from *Salmonella typhosa* were studied in patients with rheumatoid arthritis and in a normal adult to characterize further the various physiologic changes which occur following its administration.

This bacterial component elicited marked physiologic changes when administered intravenously in quantities varying from 0.01 to 0.2 μg. The minimal pyrogenic dose was approximately 0.01 μg. Marked hypotension occurred in only 1 individual, although good pyrogenic responses were elicited in all. These febrile responses were not associated with leukopenia in contrast to the occurrence of this cellular alteration following the administration of typhoid vaccine. Neither thrombocytopenia nor alterations in the differential counts were observed. This provides further evidence that leukocytes may not be the sole source of "endogenous" pyrogen. The administration of lipopolysaccharide was followed by marked changes in the levels of serum properdin, considered to be an important component in the total bactericidal capacity of serum. The properdin titer began to increase within 6 hours after injection, reaching levels 3 to 4 times the normal within 36 to 48 hours. These small quantities of lipopolysaccharide also stimulated the early production of typhoid O agglutinins to substantial titers.

Novobiocin (Albamycin): Laboratory and Clinical Studies in 30 Patients with Bacterial Pneumonia

By *Benjamin M. Limson and Monroe J. Romansky.* Department of Medicine, George Washington University School of Medicine, and the George Washington University Medical Division, District of Columbia General Hospital, Washington, D. C. (Aided by a grant from the Upjohn Company.)

Novobiocin (Albamycin) is a new antibiotic produced by *Streptomyces niveus*, an actinomycete. This agent is active in vitro against Gram-positive bacteria and certain Gram-negative microorganisms. Laboratory studies and clinical trial of the antibiotic were carried out in 30 patients with bacterial pneumonia, of whom 23 had lobar pneumonia and 7 bronchopneumonia, including 5 with bacteremia. Coexisting conditions included severe alcoholism, delirium tremens, cirrhosis, congestive heart failure, pulmonary infarction, hemiplegia, diabetes mellitus, asthma and chronic bronchitis. The diagnosis of pneumonia was established by clinical, x-ray and laboratory evidence. Smears and cultures of sputum and blood were made prior to initiation of therapy. Whenever possible, organisms isolated from cultures were typed by the Quellung method, and in vitro sensitivity tests were carried out. Concentrations of novobiocin in the blood were determined at varying intervals after cumulative oral doses. The antibiotic was given orally in doses of 500 mg. every 6 hours.

Results were satisfactory in the 30 patients. The fever subsided within 24 to 48 hours in 16 patients, and 72 to 96 hours in 10 patients. Clinical improvement was evident within 24 to 48 hours in 18 patients, 72 to 96 hours in 7 patients, and 5 to 7 days in 5 patients. In the remaining 4 the fever subsided after 5 days in 2 patients, and after 7 days in 2. Clearing of the pneumonia by physical signs and chest roentgenograms was noted within 3 to 4 days in 7 patients, 5 to 7 days in 13, 8 to 11 days in 9, and 14 days in 1 patient. Side effects in this group were limited to skin reactions in 2 patients, in the form of urticaria, which cleared up within 48 hours after cessation of therapy. These were confirmed by skin tests with the antibiotic. Serum levels of novobiocin ranged from 1.25 μg. to 80 μg./ml. at varying intervals after cumulative doses had been given. In vitro sensitivity tests on 18 strains of *Diplococcus pneumoniae* revealed 11 strains sensitive to less than 0.1 μg. novobiocin/ml., 4 to 0.2 μg., and 3 strains to 0.4 μg. The results obtained with novobiocin in the treatment of bacterial pneumonia in this series of 30 patients appear to be comparable to those obtained with other antibiotics.

KIDNEY

The In Vivo Estimation of Renal Weight in Man: Physiologic and Pathologic Aspects

By *A. P. Crosley, Jr., J. F. Brown, D. A. Emanuel, H. Tuchman, C. Castillo and G. G. Rowe.* Cardiovascular Laboratory, University of Wisconsin Medical School, Madison.

The in vivo estimation of renal weight in man has been brought about by the adaptation, in this laboratory, of the nitrous oxide determination of renal blood in combination with the Fick PAH method for the determination of total renal blood flow. Such estimations have provided a set of "normal" values (av. 379 Gm.) which compare favorably with "normal" values obtained by others at autopsy (av. 323 ± 57 Gm.). These determinations provide additional methods for studies of renal metabolism and the relationship of the latter to the tubular maximal secretory capacity for PAH (functional tubular mass, Tm_{PAH}).

The Effect of Diamox on the Carbon Dioxide Tension of the Urine

By *Nicholas Capeci, James G. Hilton, Davis Weaver and Oscar Kruesi.* Department of Medicine, St. Luke's Hospital, New York City. (Aided by a grant from the American Heart Association and the New York Heart Association.)

It is apparent from the data of several investigators that the administration of Diamox almost invariably results in a rise in the urine pCO_2. The present experiments were undertaken in an attempt to define further the mechanism by which this is brought about.

The pCO_2 of arterial plasma, renal venous plasma, and urine was determined in anesthetized normal dogs before and after the intravenous administration of graded doses of Diamox ranging from 2 to 50 mg./Kg. body weight.

Following the administration of the drug, the urine pCO_2 always rose markedly despite the fact that the pCO_2 of the arterial and renal venous plasma either did not change at all or rose only a slight degree. The renal A-V pCO_2 difference never changed significantly. The rise in urine pCO_2 after the administration of Diamox occurred in urine which was free of phosphate, and even when there was no increase in the rate of urine flow.

The changes observed appear to be explained best by the "mixing" hypothesis, whereby elevations of the urine pCO_2 occur when urines of different pH and buffer concentration are mixed together. In

this instance, however, Diamox seemed to be the major urinary buffer.

To test this hypothesis, Diamox in concentrations ranging from 1 to 10 mM/L. was added to bicarbonate solutions in vitro. Rises in pCO_2 occurred which were quantitatively similar to those obtained in the in vivo experiments.

Water and Solute Excretion in Pitressin-Resistant Diabetes Insipidus

By *Jack Orloff and Mackenzie Walser*. National Heart Institute, Bethesda, Maryland

Three otherwise normal children with congenital familial diabetes insipidus in whom urine osmolality was uninfluenced by Pitressin were studied. In these subjects variations in urine concentration during solute diuresis cannot be ascribed to antidiuretic hormone secretion, which may complicate studies in patients with pituitary or physiologic diabetes insipidus.

During control observations on normal or low sodium diets, the rate of excretion of solute-free water (C_{H_2O}) was approximately 5% of filtration rate, and urine concentration 25–65 mOsm. Solute diuresis, whether due to saline, mannitol, or acetazoleamide, was associated with a rise in both urine osmolality and C_{H_2O}. C_{H_2O} reached a maximum of approximately 12% of filtered water at high rates of solute excretion and remained essentially constant despite further increases in excretion of solute. Urine concentration reached 175 mOsm. Similar results were obtained whether filtration rate rose, fell or remained constant. Thus, the lowest rate of C_{H_2O} excretion was associated with the most dilute urine, and the highest with the least dilute urine.

It was not possible to determine whether the presence of nonreabsorbed solute per se increased C_{H_2O} since the accompanying rise in sodium excretion could be associated with enhanced reabsorption of sodium, "freeing" more water. However, the rise in C_{H_2O} with increased solute excretion may be in part attributable to osmotic restraint by nonreabsorbed solute of outward diffusion of "freed" water from a diluting segment partially permeable to water.

The data are not consistent with the theories that C_{H_2O} is formed by either the addition of a constant amount of water or the removal of a constant amount of sodium and attendant anion from isotonic tubule fluid in a water-impermeable area.

Water and Electrolyte Excretion in Rats with Diabetes Insipidus

By *Carl Alexander*. Department of Medicine, University of Minnesota, Minneapolis

Neurohypophysectomy in male rats resulted in permanent diabetes insipidus (DI) in approximately 20% of the survivors. The ratio of DI/control for average daily urine volume when on a stock diet, and water ad lib, was 7.4/L.; on stock diet, and 1% saline ad lib, the ratio was 3.5–4.0/L. The maximum daily urine volumes for DI and controls, respectively, were 142 ml. and 21 ml. when drinking water, and 305 ml. and 71 ml. when drinking saline.

During a 24-hour period of food and water deprivation, DI rats excreted more than 3 times as much water, twice as much potassium, and more sodium and chloride in the urine than did similarly treated control rats. When water ad lib without food was allowed during the subsequent 24–48-hour period, a mild temporary diuresis, followed by oliguria, occurred in both groups. Urine of DI rats contained virtually no chloride, though chloruresis followed the administration of pituitrin or Pitressin. The substitution of saline ad lib for water in the 24–48-hour period resulted in marked polyuria and polydipsia in the DI rats, and this increased fluid exchange persisted, but to a lesser degree when food was permitted and water replaced saline in the 48–60-hour interval. In contrast, saline caused only a mild diuresis in controls, which promptly was followed by oliguria with urine of high specific gravity when food and water were restored. Desoxycorticosterone acetate (DCA) reduced sodium excretion 50–60% in all rats. Potassium excretion was greatly increased in DI rats, while in controls it was reduced. Urinary pH of DI rats was increased. Water retention appeared in one DI rat while drinking saline.

A Comparison of the Renal Transport of Rubidium and Potassium

By *Arthur S. Kunin, Arlene M. Roy, Earl H. Dearborn, Belton A. Burrows and Arnold S. Relman*. Evans Memorial, Boston.

Studies from this laboratory suggest that muscle cells concentrate rubidium in preference to potassium. It was of interest, therefore, to compare the handling of these cations by the renal tubules. To this end, RbCl solutions of 25 to 100 mEq./L., labeled with Rb^{86} and made isotonic with NaCl or $NaHCO_3$, were infused into anesthetized dogs at rates of 18 to 125 μEq. Rb/Kg./min. for periods of 90 to 200 minutes.

In all experiments, as plasma Rb rose to final levels of 3 to 5 mEq./L., K concentrations were concomitantly increased, probably due to displacement of K from cells. No significant changes occurred in plasma concentration or urine excretion of Na, Ca or Mg.

Rb infusion increased K excretion and clearance. At plasma K levels of 4 to 6 mEq./L., the clearance of K (C_K) was slightly higher than at comparable plasma K levels during infusion of KCl. The ratio of Rb clearance to inulin clearance (C_{Rb}/C_{In}) varied from 0.2 to 0.9 with no relation to plasma Rb con-

centration. Mean C_{Rb}/C_K was 0.86, with 60% of the values between 0.7 and 1.0 (range, 0.2 to 1.8).

Loading with potassium thiosulfate or the administration of 500 mg./Kg. Diamox produced demonstrable K secretion (C_K/C_{In}, 1.1–1.6), and probably also secretion of Rb (C_{Rb}/C_{In}, 1.1–1.2).

The data are consistent with the view that Rb, like K, is both reabsorbed and secreted by the renal tubular cells. The relatively lower C_{Rb} might be due either to relatively increased reabsorption or decreased secretion of Rb, or both. In any case, it is suggested that the data may be explained on the assumption that renal tubular cells, like muscle cells, accumulate Rb in preference to K.

The Effects of Glutamine Loading on Renal Ammonia Excretion and Glutaminase Adaption

By *Richard Portwood and Leonard L. Madison.* Department of Internal Medicine, The University of Texas Southwestern Medical School, Dallas.

Ammonium chloride acidosis is associated with increased urinary ammonia excretion and adaptation of renal ammonia producing enzymes, especially glutaminase. These experiments were designed to determine the effect of substrate (glutamine) availability upon ammonia excretion and glutaminase adaptation in normal and acidotic rats.

Four groups of rats were studied: group 1 received the control diet; group 2, control diet plus 25 mM glutamine daily; group 3, control diet plus 5 mM NH_4Cl; group 4, control diet plus 5 mM NH_4Cl and 25 mM glutamine daily.

Daily urines were analyzed for NH_3, pH and titratable acid. After 10–14 days, the rats were killed and renal glutaminase activity determined.

Results: In the nonacidotic groups (1 and 2) there was no significant difference in renal glutaminase activity (1 = 760 ± 78, 2 = 830 ± 112). There was a significantly increased ($p < .001$) urinary ammonia excretion in the glutamine-loaded group (2 = 3.50 ± .22 mM NH_3/day) compared to control group (1 = 2.35 ± .23 mM NH_3/day).

By contrast, in the acidotic groups (3 and 4) there was no significant difference in ammonia excretion (3 = 6.62 ± .46; 4 = 6.69 ± .29 mM/day), whereas there was a significantly lower ($p < .01$) glutaminase activity in the glutamine-loaded group 3 (1278 ± 60) compared to its control group 4 (1517 ± 146).

The data show that renal glutaminase adaptation during ammonium chloride acidosis is suppressed by glutamine loading. Nevertheless, ammonia production, as reflected by excretion, remains unchanged. This, in addition to the data which show that ammonia excretion is augmented in nonacidotic rats by glutamine administration, suggests that ammonia production per unit of enzyme is augmented in vivo by glutamine loading.

Renal Arteriovenous Ammonium Difference and Total Renal Ammonium Production in Normal, Acidotic and Alkalotic Dogs.

By *J. William Poppell, F. Cuajunco, Jr., J. S. Horsley, III, H. T. Randall and Kathleen E. Roberts.* Memorial Center for Cancer and Allied Diseases. New York City.

It has been suggested that renal formation of ammonium is a continuous process even in alkalosis, and that its increased excretion in acidosis is partially due to a preferential diffusion into the acid tubular urine. To test this thesis the experiments reported here were carried out on unilaterally nephrectomized dogs to measure total renal production of ammonium and its relation to renal oxygen consumption in acidosis, and following various measures intended to elevate extracellular, intracellular and urinary pH acutely. Renal blood flow and oxygen consumption was measured by standard methods. The total ammonium produced by 1 kidney was calculated from urinary excretion, renal arteriovenous ammonium difference, and renal blood flow. The results of these studies show that there is a continuous renal production of ammonium in amounts ranging between 10–43 μEq./min. regardless of the pH of renal venous and arterial blood or urinary pH. In respiratory and metabolic acidosis total renal production of ammonium sometimes increased, as did renal venous and urinary ammonium. During metabolic and respiratory alkalosis or following the administration of potassium chloride or Diamox the urinary pH increased. However, the renal production of ammonium continued, although little of the ammonium was excreted in the urine. In all experiments the renal formation of ammonium was linearly related to renal oxygen consumption.

These results suggest that renal formation of ammonium is a continuous process and is not necessarily decreased by elevating the extracellular, intracellular or urinary pH. These findings also emphasize that quantitative evaluation of renal ammonium formation is not completely reliable if measured by urinary excretion alone, since considerable amounts of ammonium pass into the renal venous blood even when the urine is acid.

Alterations in Renal Concentrating Ability Produced by Diet

By *Franklin H. Epstein and Charles R. Kleeman.* Department of Internal Medicine, Yale University School of Medicine, New Haven.

Although the ability of the kidneys to concentrate urine in response to an antidiuretic stimulus has long been employed as a clinical index of renal function, little is known about those factors which normally condition the maximal response of the renal tubules to antidiuretic hormone. Because of the

interest surrounding their role in the treatment of renal disease, the influences upon the renal concentrating mechanism of dietary protein, urea and salt, as well as of prolonged overhydration and underhydration, were investigated.

Normal subjects were dehydrated for 12 hours and infused with Pitressin in doses (200 μ/hr.) designed to elicit a maximal antidiuretic response. After urinary concentration (freezing point) had reached its maximum, the maximal ability of the kidneys to reabsorb water free of solute (TmC_{H_2O}) was measured during a superimposed infusion of 10% mannitol which induced flows of urine between 15 and 30 cc./min.

The addition of 150 Gm. protein/day for 3 days to a diet containing less than 20 Gm. protein/day resulted in a striking increase in maximal urinary concentration (av. Δ 200 mOsm./L) and TmC_{H_2O} (av. Δ 2.2 cc./min.). Similar increases were observed when 36–48 Gm. urea/day were added for 3 days to a low-protein diet. Equimolar quantities of sodium chloride, on the other hand, did not alter renal concentrating ability. Restricting water intake for 3 days was found to enhance renal concentrating ability, whereas prolonged overhydration depressed the renal response to Pitressin. The effect of dietary protein in altering renal concentrating power was, however, clearly separable from any dehydrating tendency it might have had, since it was observed in overhydrated as well as normally hydrated subjects.

The data suggest that the maximal renal response to antidiuretic hormone is conditioned by important adaptive mechanisms called into play by changes in diet and in bodily hydration.

An Abnormality of Renal Salt and Water Conservation Characterized by Spontaneous Osmotic Diuresis: A Syndrome due to a Reversible Defect in Proximal Tubular NaCl Transport

By *Neal S. Bricker, Edmund I. Shwayri, John B. Reardan and John P. Merrill.* Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

A sustained, but ultimately reversible, renal salt and water losing state has been found in 3 patients following the relief of anuria secondary to obstructive uropathy. The large magnitude of the diuretic states, coupled with filtration rates within a range satisfactory for accurate measurements, allowed investigation of the basic mechanisms of the disorder.

The characteristics observed were those of osmotic diuresis. Thus, the inulin U/P ratios were consistently below eight (3.4 to 6.9); the urea clearances were approximately 80% of the concurrent inulin clearances; and the osmolar clearances varied from 16 to 26% of the GFR. That the unreabsorbed solutes responsible for the osmotic diuresis were sodium and chloride is indicated by the fact that these ions constituted about ⅔ of the total osmols in the urine; whereas in comparable experimental osmotic diuresis due to nonionized solutes, electrolytes constitute only ⅙ of the urinary osmols.

Sustained natriuresis and chloruresis existing in the presence of decreased filtration rates and normal plasma electrolyte concentrations can be explained only on the basis of suppression of tubular reabsorption of sodium chloride. That the fundamental abnormality was related to suppression of proximal rather than distal reabsorption is suggested: (a) by the urinary excretion of a greater quantity of sodium and chloride than could have occurred with complete suppression of distal reabsorption; (b) by the demonstration of intact distal solute reabsorption (C_{H_2O}/C_{In} = 4–10%) during the period of diuresis; and (c) by the demonstration of potassium secretion ($C_K/C_{In} > 1$).

It is concluded that the present patients exhibited sustained spontaneous osmotic diuresis secondary to suppression of tubular reabsorption of sodium chloride. The data indicate that the defect was predominantly in the proximal tubule, and there was evidence of continuing distal solute reabsorption. Re-examination of previous observations on salt-losing nephritides suggests that suppression of proximal tubular sodium chloride transport may be operative in other salt-losing states.

Tubular Function in the Recovery Phase of Acute Renal Insufficiency

By *George E. Schreiner, Leonard B. Berman and Jean Feys.* Department of Medicine, Georgetown University School of Medicine, Washington, D. C.
(Aided by a grant from the National Institutes of Health.)

The recovery phase of acute renal insufficiency affords a unique opportunity to study the regeneration of a highly complex cell—the epithelium of the renal tubule in the human subject. The present report concerns studies made over a 3-year period. A specific tubular function—reabsorption of water against a concentration gradient—was studied by means of osmotic U/P ratios determined on timed clearance periods after 24 hours of a dehydration diet and again after the administration of antidiuretic hormone.

Eleven control subjects have shown a maximum osmotic U/P ratio ranging from 3.22 to 4.24, with a mean of 3.73. The highest urine solute concentration recorded on this test has been 1238 mOsm./L. In 16 patients recovering from acute renal insufficiency, the average maximum U/P ratio obtained within the first 30 days was 1.33. All observations in the first 10 days were below 1.25. Ten repeat studies have been obtained in the same patients from 10 to 60 weeks after onset of diuresis. Average maximum U/P osmotic ratio in this group is 2.9. Serial studies

obtained in highly cooperative patients have shown a rapid phase of improvement over 6 to 10 weeks, and then a slow phase lasting over many months. Some patients are still improving at the end of a year.

The data demonstrate a severe form of nephrogenic diabetes insipidus following acute renal insufficiency. Renal biopsies have demonstrated reepithelization of renal tubules and increases in the height of tubular cells. Regrowth of epithelium has been accompanied by progressive increase in the ability to reabsorb water against a concentration gradient. The test has important diagnostic value in cases with transient or undocumented oliguria, combined lesions, or associated obstructive uropathy, or where there is any doubt concerning the underlying pathologic entity.

Serial Renal Biopsies and Function in Acute Glomerulonephritis

By *Alvin E. Parrish and John S. Howe.* V. A. Hospital and The George Washington University, Washington, D. C.

Eleven patients with acute glomerulonephritis have been followed for periods up to 3 years with repeat renal needle biopsies, renal functions as measured by urea clearance and PSP excretion, and careful examination of urinary sediment. Seven of the 11 patients have had, in addition, serial determinations of inulin and PAH clearances during the course of their disease.

The initial renal biopsy was from 5–35 days (av. 19 days) from the onset of symptoms of renal disease. The changes seen on biopsy in less than 14 days showed an increase in glomerular size and endothelial proliferation in all patients studied (5 out of 5); decrease in capillary lumen size, polymorphonuclear leukocyte infiltration and adhesions between glomeruli and Bowman's capsule in 3 of 5 patients; and thickening of the basement membrane in 2 of 5 patients. In the earliest biopsies the tubular epithelium was swollen and vacuolated, later biopsies revealed dilated tubules with flattened epithelium. Biopsies done 20–40 days after the onset revealed cellular proliferation and thickening of the basement membrane in all 8 patients studied, polymorphonuclear leukocyte infiltration in 5 out of 8 and dilated tubules in 4 out of 8 patients. After 40–60 days, thickening of the basement membrane and increased cellularity of the glomeruli was still the predominent lesion. These findings were present at all subsequent biopsies up to 3 years after the onset, but with a decreasing degree of cell proliferation. At 3 years the most striking finding was thickening of the basement membrane.

The clinical status of the patients was always better than would be expected from the biopsy. The urinary sediment and renal functions correlated more with the pathologic condition present than with the clinical status of the patient.

Effect of Orthostasis on the Urinary Excretion of Plasma Proteins and Dextrans in Patients with Proteinuria

By *Alfred W. Childs, Burton Combes, Henry O. Wheeler and Stanley E. Bradley.* Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York City.

Following assumption of the upright position, the proteinuria of renal disease decreases roughly in proportion to the fall in glomerular filtration rate and renal blood flow. All moieties of the urinary protein appear to be equally affected, since no gross change in paper electrophoretic pattern of urinary proteins has been observed. However, small but significant alterations may have escaped detection, and it seemed of importance therefore to follow changes in individual protein fractions by more accurate methods.

Clearances of plasma protein fractions were measured before and during orthostasis in 4 patients with proteinuria. Protein fractions were determined by paper electrophoresis and fractional dye elution, and total protein concentrations by the biuret method. The PAH clearances were followed throughout, as a measure of hemodynamic responses. Inulin clearances were determined in the late recovery phase.

With orthostasis, the excretion of individual protein fractions decreased proportionately. Combined albumin and α_1 globulin clearance fell by 24% on the average, α_2 globulin 34%, β globulin 27%, and γ globulin 26% in 3 subjects. Clearances did not change in one subject with far advanced renal disease and uremia.

The clearances of protein fractions varied in relation to molecular weight, as other workers have shown. The clearance of clinical dextran (anthrone method) decreased in proportion to the fall in protein clearance during orthostasis. Analysis of dextran molecular fractions (method of Wallenius) in the urine of these subjects suggested a correlation between molecular size and clearance. Dextran molecular weights in excess of 60–70,000 were not detected in the urine, confirming similar observations by Wallenius, and suggesting that the globulins escaping in the urine in renal disease may not be comparable dimensionally to electrophoretically similar globulins in the plasma.

Defense of Intracellular Electrolyte Composition during Experimental Nephrotic Edema

By *Jack Metcoff, Jorge Martner, Irena Antonowicz and John Craig.* Boston

Since the nephrotic syndrome can be induced by injection of an aminonucleoside into immature rats, the present studies on nephrotic edema were designed to determine whether: (1) increased ex-

tracellular sodium obligates simultaneous accumulation of intracellular sodium; (2) superimposed diet potassium depletion favors accumulation of intracellular sodium in excess of that expected from potassium deficiency alone; and (3) loss of body potassium exceeds that derived from tissue protein catabolism.

In one group, the nephrotic syndrome was studied during accumulating edema on a diet containing no potassium and restricted sodium; in another group, following maximal edema, the nephrotic renal lesion was sustained by continued aminonucleoside injection, but a sodium-free intake with added carbonic anhydrase inhibitor (Diamox) was initiated. Analyses of the electrolyte, H_2O and noncollagen nitrogen content of whole skin, carcass and viscera, and of muscle samples of young rats with the nephrotic syndrome, were compared with those from non-nephrotic pair-fed controls.

With increasing edema superimposed on malnutrition and severe dietary potassium deficiency, extracellular fluid was slightly hypertonic, but $[K + Na]_{ICW}$ was about 20–30 mEq./L. less than $[Na + K]_{ECW}$. The potassium content of surviving muscle cells was not significantly reduced, although expansion of ICW effectively reduced $[K]_{ICW}$. Cell sodium also remained normal, in contrast to characteristically increased amounts observed in pair-fed non-nephrotic potassium deficient rats.

Sodium-free diet with Diamox induced diuresis despite continued aminonucleoside administration. After diuresis, the nephrotic rats had reduced cell solids relative to controls. Diminished total body potassium reflected depletion of cell protein, since K/NCN was 3.4 in both groups.

If sodium does not accumulate intracellularly, and endogenous potassium is available from tissue catabolism, cell potassium is sustained despite dietary potassium deficiency, indicating that cell membrane and probably transport integrity are unusually well-defended during this type of malnutrition and edema.

On a New Pathologic State Associated with the Nephrotic Syndrome in Adults

By *Robert M. Kark, Victor E. Pollak, Conrad L. Pirani and Robert C. Muehrcke.* Departments of Medicine, Presbyterian Hospital, Cook County Hospital, and the Research and Educational Hospital, and the Department of Pathology, University of Illinois College of Medicine.

In the course of a study of the nephrotic syndrome by percutaneous renal biopsy, we have encountered 5 patients in whom the histologic appearances of the kidney were unusual. Their ages ranged from 15 to 82 years. They presented a history only of the gradual onset of edema, and edema was the only positive physical finding. All had massive proteinuria, hypoalbuminemia, and hypercholesterolemia; and casts and oval fat bodies were found in the urine.

Study of the renal biopsy specimen revealed neither proliferative changes nor thickening of the glomerular basement membrane, which was thin and delicate. The glomerular tufts were intensely congested, in contrast to normal biopsy material, in which only a few erythrocytes are seen in each glomerular tuft. There was severe tubular degeneration and much interstitial edema. The absence of changes in the glomerular basement membrane contrasts with the findings of autopsy studies of adults dying with the nephrotic syndrome.

When treated with ACTH these patients had an excellent diuresis. During the diuretic phase a second biopsy was made in 2 patients. The previously congested glomeruli now contained a normal number of erythrocytes, and the basement membranes were normal. The tubules were healthier, and the tubular epithelium was taller than in the oliguric phase. The interstitial edema had disappeared.

The prognosis has been good in these patients. All are alive; none is in renal failure. The response to ACTH and the prognosis are better than in patients with membranous glomerulonephritis, and severe glomerular changes have not developed in any of these 5 patients. This condition may be similar to the lipoid nephrosis which occurs in children.

The Effects of Infusion of Salt-Poor Human Serum Albumin on Serum Cholesterol Cholinesterase, and Albumin Levels in Healthy Subjects and in Patients Ill with the Nephrotic Syndrome.

By *John A. Soothill and Robert M. Kark.* Department of Medicine, Presbyterian Hospital, Cook County Hospital, and University of Illinois Hospitals, Chicago.

Previous investigations have demonstrated in man relationships between albumin and serum cholinesterase which—like cholesterol—are synthesized mainly by the liver. Infusion of salt-poor human serum albumin (HSA) suppressed hepatic synthesis of cholinesterase (CHe) and presumably albumin. Increased albumin synthesis in the nephrotic syndrome was associated with high levels of CHe, while depression of albumin synthesis in hepatic diseases and malnutrition was associated with decrease in CHe.

We have also observed parallel changes of CHe and cholesterol levels in the nephrotic syndrome (increase); in malnutrition (decrease); and in hepatocellular dysfunction (decrease). This report, therefore, describes experiments on man, designed to study interrelationships between serum albumin, CHe and cholesterol.

Fifty Gm. HSA were infused daily into healthy men and nephrotic patients living on fixed regimes on a metabolic ward. Studies were made during 3 9-day periods: pretherapy, therapy and post-

therapy. Measurements were made of serum protein and protein partitions, serum cholinesterase, serum cholesterol and cholesterol partitions, hematocrit, prothrombin, fibrinogen, urine volume, urinary protein and protein partitions. Observations were made of urinary casts. In healthy subjects during HSA infusion, albumin increased to ±6.5 Gm./100 ml., and albumin and hyaline casts appeared in urine. Cholesterol levels fell from the order of 200 to 120 mg./100 ml., and CHe from 1.1 to 0.76 Δ pH U/hr. The decline in these serum moieties and return to normal showed smooth curves. There was no significant change in body-weight or hematocrit.

HSA infusion into nephrotic patients caused a diuresis and rising albumin levels (from approximately 2.5 to 4.5 Gm./100 ml.) and a 50% reduction in CHe and cholesterol.

These observations suggest parallel and interrelated hepatic synthesis of serum albumin, cholinesterase and cholesterol, which explain the high levels of cholesterol and CHe so commonly seen in the nephrotic syndrome.

Steroid Therapy in the Nephrotic Syndrome

By *Howard C. Goodman, James H. Baxter and Hans Keitel.* National Heart Institute, Bethesda, Maryland

Nine adults and 9 children with the nephrotic syndrome were treated with steroids, usually 40 mg. prednisone or 160 mg. hydrocortisone daily for 1 to 2 months. Serial measurements were made of urinary sediment and protein, and serum proteins, lipids and electrolytes. Seven adults and 7 children had remissions which were complete except for residual proteinuria in 1 child and 3 adults, and moderate proteinuria and hypoproteinemia in 2 other adults. Two adults and 2 children subsequently relapsed.

Little difference in side effects of prednisone and hydrocortisone was noted in these patients with restricted sodium intake. One hypertensive child, whose course had been steadily downhill, developed malignant hypertension co-incident with therapy; otherwise, hypertension with steroid therapy was not a serious problem. Except for this case and 1 nephritic (not included here) who developed a bleeding ulcer, no side effects serious enough to preclude continuing therapy occurred. We were impressed by the frequency of temporary psychic disturbances and facial and generalized rashes which occurred upon decreasing or discontinuing therapy.

In 6 patients measurements were made of the degree of suppression by steroids of the skin inflammation produced by intradermal injections of serial dilutions of tuberculin (PPD). Correlation between steroid suppression of inflammatory response to PPD and suppression of the renal lesion was poor. One patient had marked suppression of the inflammatory response with no change in the nephrotic syndrome, while another patient who showed minimal suppression of the inflammatory response had a complete remission. As measured by suppression of inflammation and other indices of steroid activity, the effects of 40 mg. prednisone were equivalent to those of 160 mg. hydrocortisone.

Intrarenal Hemodynamic Adjustments and Urinary Protein Excretion in Patients with Renal Disease

By *Willoughby Lathem.* V. A. Hospital, West Haven, Connecticut

Experimental observations suggest that the rate at which protein molecules pass across capillary membranes is influenced under conditions which change intracapillary hydrostatic pressure and the rate of blood flow through the capillaries. In the present investigation a study of these factors on glomerular permeability to protein was made in patients with proteinuria due to renal disease.

Total and individual (paper electrophoresis) plasma and urinary protein levels were measured before, during and following: (a) infusions of l-norepinephrine sufficient to elevate systolic blood pressure 25–50 mm. Hg, (b) infusions of l-epinephrine which elicted renal vasoconstriction but which did not elevate blood pressure, (c) infusions of ephedrine which elevated blood pressure but did not alter renal hemodynamics, and (d) following intravenous l-hydrazinophthalazine. The response to l-norepinephrine and l-epinephrine was similar. Plasma proteins did not change. Total urinary protein output increased in association with a reduction in renal plasma flow (RPF), a constant glomerular filtration rate and a rise in the filtration fraction. The output of each protein fraction increased proportionately. On recovery, protein excretion returned towards control levels. Ephedrine and Apresoline did not affect protein output consistently.

These results indicate a correlation between the increased protein excretion and the renal vasoconstriction elicited by the adrenal medullary hormones and suggest that either a change in intraglomerular pressure (as judged by the filtration fraction) or a reduction in RPF, or both, modified the filtration and/or diffusion of protein molecules through the glomerular membrane.

The Pathogenesis of Anemia in Chronic Renal Disease

By *R. B. Chodos.* Radioisotope Service, V. A. Hospital, and the Department of Medicine, State University of New York College of Medicine, Syracuse.

Previous reports suggest that anemia in chronic renal disease may result from impaired blood formation, increased blood destruction, or a combination of these 2 processes. Usually one aspect has

been studied quantitatively, while conclusions regarding the role of the other process have been reached by inference.

This investigation has been undertaken to evaluate both blood formation and destruction in the anemia of chronic renal disease. Blood formation in 7 such patients has been estimated using Fe^{59} to determine the plasma and red cell iron turnover rates and the ferrokinetic pathways. Blood destruction was evaluated by determining the autosurvival of Cr^{51}-tagged red cells. In 1 instance survival of cells from a patient with chronic renal anemia was evaluated both in the patient and in a normal recipient.

With 1 exception the red cell iron incorporation and the red cell iron turnover rate indicated a significant depression of blood formation. External measurements over the precordium, liver, spleen and bone marrow revealed an initial accumulation of iron in the marrow. Subsequently, a substantial quantity of iron concentrated and remained in the liver. A similar hepatic accumulation has been observed in aplastic anemia.

Red cell survival was only moderately decreased in several patients, and this was not a consistent finding in all cases. It is noteworthy, however, that the tagged red cells of 1 patient with chronic renal anemia showed a decreased survival in the same patient but a normal survival when infused into a healthy recipient.

Sequential blood formation and red cell survival studies indicate that diminished blood formation, decreased red cell survival, or both, may be implicated in the anemia of chronic renal disease. Decreased red cell survival is probably related to an unknown factor in the internal environment of the patient rather than to a defect of the patient's red cells.

Changes in Renal Hemodynamics during Normal Pregnancy

By *Ezra Sohar, Eugene Scadron and Marvin F. Levitt.* Mount Sinai Hospital, New York City

Glomerular filtration rate (GFR), renal plasma flow (RPF) and TmPAH were measured by standard technics in 18 women between the 14th and 41st week of pregnancy. No patient gave a previous history of hypertension or of specific toxemia of pregnancy, and elevation of blood pressure was not noted during the pregnancy under observation.

The middle trimester was characterized by consistently supernormal GFR's and RPF's, averaging 180 cc./min./1.73 $M.^2$ and 900 cc./min./1.73 $M.^2$, respectively. Both these values exceeded the expected normal in nonpregnant women by 50%, the filtration fraction remaining at the normal figure of 20%. At approximately the 26th week of pregnancy, a progressive fall in RPF toward normal occurred, despite persistence of the supernormal GFR's. This period was therefore characterized by a progressively increasing filtration fraction, reaching 28–30%. Near term the filtration rate tended to return toward the mean for normal nonpregnant women, but remained above expected values. Values for TmPAH fell within the normal range throughout pregnancy.

These data suggest that in the third trimester of pregnancy a conspicuous reduction in the caliber of the renal afferent and efferent arterioles occurs. This reduction in arterial caliber appears to be superimposed upon a renal vascular bed previously subject to considerable afferent dilatation. It may be relevant that the alterations typical of the third trimester of normal pregnancy at least qualitatively mimic those characteristic of nonpregnant subjects with essential hypertension.

Serial Studies of Renal Function Throughout Pregnancy and the Puerperium in the Normal Woman

By *Ethan A. Sims and Kermit E. Krantz.* Departments of Medicine and Biochemistry and Obstetrics and Gynecology, University of Vermont College of Medicine, Burlington.

In view of the contradictory results of previous studies of renal function in pregnancy, we have carried out serial studies in 12 pregnant subjects and duplicate studies in 9 control subjects.

The technic of constant infusion of inulin and of para-aminohippurate was used for determination of glomerular filtration rate (GFR) and of renal plasma flow (RPF) in 85 clearance studies at approximately monthly intervals starting at the 10th to the 25th weeks, and the results were evaluated by accepted methods of statistic analysis.

It was found that: The RPF (and renal blood flow) was significantly elevated to a maximum at the 16th week of 820 ml./min. (s.d. 99 ml./min.). A significant elevation persisted through the 13th week, falling to the normal range at term, and dropping significantly below the normal range for a variable number of weeks (up to 25 weeks in 5 subjects) before returning eventually to the normal range.

The GFR remained significantly elevated to a maximum of 166 ml./min. ± 19 ml. from the 15th week through term, but returned to the nonpregnant range early in the puerperium. The filtration fraction was significantly elevated (0.20 to 0.25) until term, varying reciprocally with the RPF.

Consistent with these changes in the filtration rate, the mean blood urea nitrogen from the 10th week to term was 8.5 mg./100 ml., with the relatively small s.d. of ± 1.5 mg., as opposed to 13 mg./100 ml. ± 3 mg. in the control group. Similarly, serum creatinine (Hare method) had a mean of 0.45 mg. ± 0.07 mg. from the 15th through the 35th weeks, as opposed to 0.66 mg./100 ml. ± 0.07 mg. for the controls.

In the control group, measurements of RPF were significantly higher when repeated, and in the experimental subjects apprehension apparently further invalidated the initial measurements. For this reason only, second and later measurements were used for calculation.

These deviations from the accepted normal values must be taken into account in studies of both normal and pathologic pregnancy.

The Histology and Natural Repair of the Renal Lesions of Pre-Eclampsia

By *Victor E. Pollak, John B. Nettles, Conrad L. Pirani, Robert M. Kark and Robert C. Muehrcke.* Departments of Medicine, Obstetrics and Pathology, University of Illinois College of Medicine, and the Departments of Medicine, Presbyterian Hospital, the Research and Educational Hospital, and Cook County Hospital, Chicago.

As toxemia of pregnancy is rarely fatal, little is known of its renal pathology. This report, therefore, correlates the pathology of renal tissue obtained by percutaneous needle biopsy with the clinical aspects of the syndrome. Twenty-five patients with hypertension in late pregnancy were studied; most had edema and/or proteinuria. Twelve were restudied postpartum.

The kidney of 1 patient was normal; another had chronic glomerulonephritis and acute pyelonephritis. The remaining 23 patients were divided into 3 groups:

Group 1: A singular lesions was observed in 15 patients ill with pre-eclampsia. The glomeruli were swollen and ischemic. Their basement membranes were widened throughout each glomerulus and involved equally all glomeruli. This change was due to swelling or edema and was *not* the result of increased deposition of mucopolysaccharide material (PAS staining) on the basement membrane. It could be distinguished, therefore, from membranous glomerulonephritis. Mild degenerative changes were seen in the tubular epithelium. Proteinaceous material was found in Bowman's spaces and tubular lumina. The interstitial tissue and vessels were normal.

Four patients were restudied postpartum. They were well, and the histologic changes in the kidney had reverted to normal. A fifth patient had eclampsia and convulsions. A "pre-eclamptic" renal lesion was found; it was more pronounced 6 days postpartum.

Group 2: In 4 patients the disease was clinically similar to group 1, but areas of membranous thickening were noted in addition to the swelling of the basement membrane. There was mild sclerosis of small arteries and arterioles. Postpartum, the glomeruli were normal in 1; in a second, basement membrane thickening had persisted. The arteriolar sclerosis had not changed.

Group 3: Vascular sclerosis, but no swelling of the glomerular basement membrane was noted in 4 patients.

The Relationship of Bacterial Species to the Pathogenesis of Hematogenous Pyelonephritis

By *A. I. Braude, A. P. Shapiro and J. Siemienski.* Department of Internal Medicine, the University of Texas Southwestern Medical School, Dallas.

Although several bacterial species may produce pyelonephritis, their specific roles in its pathogenesis are obscure because human kidneys are examined only rarely during early stages of the disease. An experimental model of human hematogenous pyelonephritis was therefore employed to study variations in pathogenesis in rats inoculated with 4 different species isolated from patients with pyelonephritis. After inoculating bacteria intracardially, the kidneys were massaged through the intact abdominal wall and the rats killed 4 to 6 weeks later.

All species produced pyelonephritis, but lesions were most severe with *Proteus mirabilis* which also induced renal stones ($Mg\ NH_4PO_4$) in 3 of 13 rats. This species produced mild hypertension in 3 rats, but no relationship existed between blood pressure and severity of pyelonephritis. Marked renal destruction also resulted from infections by *Escherichia coli* and *Pseudomonas aeruginosa*, and least from enterococci (*Streptococcus zymogenes*). Yet, renal cultures at 6 weeks yielded a far heavier growth of enterococci than Gram-negatives which had frequently disappeared from the kidneys by then. The inflammatory reaction initiated by Gram-negatives often persisted, however, after infection had vanished.

Although renal massage was essential for a high incidence of pyelonephritis with all Gram-negatives, enterococci, by contrast, readily established both renal infection and, to a lesser extent, renal lesions in animals not subjected to renal massage. Existing pyelonephritis by *E. coli*, however, often prevented superinfection by enterococci.

These results suggest that although enterococci more readily establish lasting infections in the kidney, they are less destructive than Gram-negative organisms.

LIVER

The Effect of Chlorpromazine on the Excretion of Bromsulphalein (BSP) in Human Bile

By *Irwin M. Arias, Oscar M. Jankelson and Norman Zamcheck.* Boston City Hospital, Boston

Although jaundice has been attributed to chlorpromazine administration, no consistent effect on hepatic or biliary function has been demonstrated in man. Significant delay in BSP excretion in bile occurred after chlorpromazine injection in 6 subjects in the following experiments:

(1) The bile output of a hydrated, nonjaundiced patient with complete biliary obstruction was collected from a draining cholecystostomy. Following chlorpromazine (50 mg. i.m.) there was a 10-minute delay in the appearance of BSP (5 mg./Kg. i.v.) in bile without significant alteration in the biliary bilirubin concentration. Dehydration similarly delayed BSP excretion, but significantly increased bilirubin concentration in the bile.

(2) Hepatic ("C") bile was collected every 5 minutes from 5 normal subjects through a Miller-Abbott tube in the duodenum. (a) Three subjects received a single dose of BSP (5 mg./Kg. i.v.); BSP first appeared in the duodenum at 15 minutes. The procedure was repeated several days later and chlorpromazine (50 mg. i.m.) was given 30 minutes before the BSP; dye appeared in the duodenum between 30 and 35 minutes in each. (b) Two subjects received intravenous BSP infusions at a constant rate of 6 mg./ml./min. After stabilization of plasma and bile BSP concentrations, chlorpromazine (50 mg. i.m.) was injected. In both subjects, BSP concentration in the duodenal contents began to fall in approximately 30 minutes; fell to ⅓ of the initial concentration by 1 hour and rose to the prechlorpromazine levels by 2 hours.

In each experiment chlorpromazine did not significantly affect plasma BSP clearance or bilirubin concentration in the duodenal contents.

Chlorpromazine (50 mg. i.m.) did not alter urinary excretion of BSP (5 mg./Kg.) in 2 subjects. In vitro, it neither bound BSP nor affected BSP uptake by guinea pig liver slices.

These studies indicate that chlorpromazine interferes with BSP excretion by the hepatobiliary system. It is suggested that the site of this action is at the hepatic cellular level.

Observations on the Metabolism of Vitamin B_{12} in Patients with Liver Disease

By *Thomas D. Stevenson and Marion F. Beard.* University of Louisville School of Medicine, Louisville.

Elevation of the serum vitamin B_{12} level has been reported in patients with liver disease, and this finding has been confirmed in our laboratory. Serum levels and urinary excretion of vitamin B_{12} have been determined by microbiologic assay utilizing *Euglena gracilis* as test organism. Elevated levels of serum vitamin B_{12} have been found only in patients with hepatic parenchymal disease, i.e., alcoholic cirrhosis and infectious hepatitis. The serum level of vitamin B_{12} is markedly elevated in patients with hepatic coma. Increased levels of vitamin B_{12} have not been found in patients with obstructive jaundice.

The increase in serum vitamin B_{12} could not be correlated with any single test of liver function. The serum level and the urinary excretion of vitamin B_{12} are not influenced by dietary restriction of the vitamin in patients with liver disease, and increased urinary excretion of vitamin B_{12} cannot be consistently demonstrated in these patients. The presence of normal levels of serum vitamin B_{12} in the portal venous blood of patients without liver disease obtained during laparotomy, and the presence of elevated B_{12} levels in patients with infectious hepatitis, indicates a portosystemic shunt is unlikely as a factor in producing the elevated B_{12} levels in these patients. Observations on a limited number of patients indicate that the serum vitamin B_{12} level returns to normal, parallel with clinical improvement, and there is evidence suggesting that the level of vitamin B_{12} may be influenced by the administration of folic acid. In a single experiment in a patient with liver disease the plasma clearance of intravenously administered Co^{60} radioactive vitamin B_{12} was normal. The evidence suggests that the elevation of the serum level of B_{12} in patients with liver disease represents the release of the vitamin from hepatic cells.

Serum Glutamic Oxalacetic Transaminase: A Sensitive Test for Hepatic Cell Damage

By *H. E. Ticktin, J. H. Epstein and B. H. Ostrow.* George Washington Hospital, The George Washington University Medical Division, The District of Columbia General Hospital, and the George Washington University School of Medicine, Washington, D. C.

Wroblewski observed elevated serum glutamic oxalacetic transaminase (GOT) in active hepatocellular damage. The present study confirms these findings and presents random GOT assays in 36 cases of liver disease. GOT was determined spectrophotometrically by the method of Karmen, Wroblewski and LaDue. The range is 5 to 33 U/ml.

Of the 21 cases with cirrhosis, 18 were portal, 2 biliary and 1 cardiac. Those cases with active hepatocellular damage by clinical appraisal (fever, jaundice, liver tenderness, ascites) and abnormal hepatic function tests, showed elevated GOT. The average level was 105 U/ml. In the cases clinically appraised as inactive, but with abnormal hepatic function tests, GOT averaged 34 U/ml.

Five patients had infectious viral hepatitis. All had elevated GOT levels; the average was 94 U/ml. Elevated GOT assays have also been observed in gangrene of the liver (highest level observed in our

laboratory), and in methyl testosterone-induced toxic hepatitis.

There were 2 cases of biopsy-proven cholangitis. GOT rose to 144 U/ml. in the case with active disease but was normal in the case with chronic involvement.

Three cases of extrahepatic obstructive jaundice were studied. GOT levels were persistently normal during the icteric phase of illness. Levels of GOT were elevated during active hemolysis of acquired hemolytic anemia and in 1 case of Gaucher's disease.

It is our impression that serum glutamic oxalacetic transaminase is a sensitive indicator of active hepatic cell damage. Its serial determinations may be of value in the prognosis of liver disease.

A Clinical Study of the Serum Glutamic Oxalacetic Transaminase in Liver Disease

By *Robert E. Dutton, Robert D. Lindeman, Lionel A. Rudolph and Richard H. Lyons.* Department of Medicine, State University of New York, College of Medicine, Syracuse.

The levels of serum glutamic oxalacetic transaminase were followed in 138 patients with various types of liver disease for periods up to 6 months. Concomitant clinical evaluation and liver function tests were obtained.

Sixty-six cases of cirrhosis, studied on 70 hospital admissions, were divided into 3 groups according to the presence or absence of jaundice and ascites. On admission, the level of transaminase varied widely in each group from normal to a marked elevation. The trend during hospitalization in each group was toward normal levels. In individual cases, the transaminase continued to rise during the first 2 to 4 weeks after admission. Fourteen cases of extrahepatic bile duct obstruction also showed widely varying levels of transaminase, with no correlation to the serum bilirubin level being demonstrable. Our experience was that the transaminase level does not provide a valid differentiation between obstructive jaundice and jaundice due to hepatocellular damage.

Nine patients with acute cholecystitis had elevations within 48 hours after onset of symptoms. Five of these had no icterus. Since patients with myocardial infarction have been shown to have an elevated transaminase within 48 hours after infarction, it would appear that this test would not aid in the differentiation between acute cholecystitis and myocardial infarction.

Twenty-five cases of hepatitis of viral origin showed peak elevations between the third and fifth day after onset of symptoms, tending to start their return toward normal with the onset of jaundice. The more severely ill patients had a more persistent elevation of transaminase. Its return toward normal was followed by clinical improvement in the great majority of patients. A marked elevation of transaminase was noted during the incubation period and shortly prior to the onset of symptoms in infectious hepatitis. Minimal elevations were noted in the end-stage of acute yellow atrophy. Therefore, it would appear that a minimally elevated transaminase does not necessarily indicate a good prognosis in patients with hepatitis.

Diiodotyrosine and Triiodothyronine Metabolism in Liver Disease

By *W. R. Ruegamer and R. B. Chodos.* Radioisotope Service, V. A. Hospital and Departments of Biochemistry and Medicine, State University of New York College of Medicine, Syracuse, New York.

Since we have demonstrated previously in animal and in vitro experiments that the liver is the principal deiodination site for diiodotyrosine (DIT) and triiodothyronine (T_3), a study has been made of the metabolism of these substances in individuals with liver disease. Carrier-free doses of 100 μc. of DIT and T_3 were injected intravenously into 50 normal individuals and patients with cirrhosis. The disappearance of I^{131} activity was followed for 7 to 10 days from whole blood, whole plasma and fractionated plasma into the saliva, urine and thyroid. Samples of saliva, urine and plasma trichloracetic acid filtrates were chromatographed in several solvent mixtures, and the relative concentrations of all I^{131}-tagged substances were determined by counting the chromatographs in a scintillation well counter.

Whole plasma half-time values averaged 9.5 hours in normal subjects and 16.6 hours in patients with cirrhosis receiving DIT, whereas values of 30.1 and 34.4 hours, respectively, were obtained for similar groups of patients receiving T_3. Paper chromatographs of urine specimens revealed that relatively large amounts of DIT and T_3 passed into the urine of patients with cirrhosis, whereas 90–100% of the total I^{131} activity excreted by normal individuals appeared as iodide. In the case of T_3, the per cent of total plasma activity occurring as nonprotein precipitable I^{131} reached a maximum of 20–40% in approximately 12 hours, after which it declined slightly. Chromatographic analysis of this fraction revealed that a significant portion of I^{131} activity was T_3, and that the remainder was iodide. Salivary clearances for iodide were calculated from the plasma and saliva chromatographic data, and these were found to be constant in both groups. It is concluded that in liver disease, DIT and T_3 are deiodinated less rapidly and completely than in normal subjects.

Serial Studies of Portal Venous Pressure in Acute Hepatitis

By *Stanley Reichman and William D. Davis, Jr.*

Percutaneous measurements of intrasplenic pulp pressure have been reported and verified by us

and others as a reliable guide to existing pressures in the portal circulation in the same patient. Using an adaptation of the Burch phlebomanometer, serial intrasplenic pulp pressure measurements were recorded in 33 patients with acute viral hepatitis with jaundice. Initial readings were made at the height of the illness, and convalescent readings were taken when evidence of full recovery was available. The latter served as controls for each patient. Esophagoscopy was performed during the acute stages in 23 of these patients, and a careful search for esophageal varices was made.

The results of these studies have shown that in 29 of 33 patients there was a consistently higher pressure reading (mean 142 mm. H_2O) at the height of the jaundice than during the convalescent stages (mean 96 mm. H_2O). The initial readings were usually not above the normal range (40–200 mm. H_2O). However, 5 patients had readings over 200 mm. H_2O (210–230 mm. H_2O) and 6 patients had high normal readings (160–200 mm. H_2O). These findings were correlated with the fact that no esophageal varices were demonstrated at esophagoscopy. All convalescent measurements were well within the normal range. In addition, the height of the initial pressure was not found to be related to the severity of the illness, the degree of jaundice or hepatic or splenic enlargement.

It is concluded that though the acute inflammatory process results in increased intrasplenic pulp pressure, it is generally not above the normal range. It is conceivable that this elevation, which returns to normal during convalescence, is caused by sinusoidal obstruction.

One patient, not included in the above group, showed a continued elevated reading during convalescence (over 200 mm. H_2O); liver biopsy, prompted by this finding, revealed progression to a chronic phase of hepatitis.

Zinc Sulfate Turbidity Test as an Aid in the Diagnosis of Hepatobiliary Disease

By *Thomas E. Wilson, Charles H. Brown and Adrian Hainline, Jr.*

To determine the value of the zinc sulfate turbidity test (ZST) as an aid in the diagnosis of hepatobiliary disease, 1187 tests were reviewed and compared with the clinical diagnosis. The results of the ZST are expressed in units, with 4–12 units being the limits of normal at the Cleveland Clinic.

Of 392 cases diagnosed as "normal" only 9 were above 12 turbidity units. The mean value was 6.42 U with a standard deviation of ±2.54. Of 494 cases with a diagnosis of organic disease of a noninfectious, nonhepatic type, 57 were elevated above 12 U. The mean value was 7.82 ± 7.28 U. Twelve patients had values of 19 U or higher, and of these, 4 had chronic ulcerative colitis, 3 rheumatoid arthritis, and 1 each had hemolytic anemia, myelofibrosis, lymphoblastoma, essential hypertension and nephritis. All of these diseases are associated with an increased serum γ globulin, accounting for the elevated ZST and demonstrating that the ZST is not specific for liver disease alone. Of 179 cases of cirrhosis, including both postnecrotic and Laennec's, the ZST was elevated in 118. The mean value was 17.19 ± 8.81 U. Of 54 cases of hepatitis, 20 were elevated. The mean value was 11.8 ± 4.69 U. Of 42 cases of obstructive jaundice, only 4 were elevated. The mean value was 6.86 ± 3.85 U.

The results obtained in the "normal" group were compared with the values of the "cirrhotic" group and a significant difference (T value) of 16.07 was found. When the results of the normal group were compared with the hepatitis group, a T value of 8.26 was found. These figures indicate that the ZST is a valuable test in the diagnosis of hepatobiliary disease and is of value in the diagnosis of chronic liver disease (cirrhosis). The ZST is more frequently positive in cirrhosis than are other flocculation tests. When normal in long-standing jaundice, it is a nearly specific indication of a surgical cause of the jaundice.

Hepatic Cirrhosis: Impending Hepatic Coma and Increased Blood Ammonium Concentrations during Protein Hydrolysate Infusions

By *Leslie T. Webster, Jr.* Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Service, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Ammonium metabolism during intravenous protein hydrolysate administration was studied in 4 patients with cirrhosis.

During rapid infusions of 2 different hydrolysates to 2 patients, both developed confusion and the tremor characteristic of impending hepatic coma. Venous blood ammonium concentrations promptly increased 3 to 5-fold, probably because of the large quantity of ammonium infused (NH_4-N comprised 7.2–7.9% of the total nitrogen present in these hydrolysates). Thus, in susceptible patients with cirrhosis, the rapid parenteral administration of protein hydrolysate may induce impending hepatic coma which, in similar patients, may follow protein ingestion.

On separate occasions the 2 other patients received solutions of an acid hydrolysate of fibrin (5% Aminosol) and of dl-alanine (3.7–4.2%) at slow constant infusion rates with only delayed venous blood ammonium rises (60–75 min.). However, NH_4Cl solutions, providing NH_4-N equal to or less than that analyzed in Aminosol, produced prompt rises (15 min.), while NH_4Cl solutions providing NH_4-N equaling the small amount analyzed in the alanine solutions did not. Therefore, the delayed venous blood ammonium increases during the

Aminosol and alanine infusions probably resulted from deamination of the infused amino acids.

In further studies, l-glutamine and l-asparagine, 2 amides in Aminosol, yielded little NH_4-N on analysis. In 1 patient, a concentration of NH_4Cl, which alone produced a prompt rise in venous blood ammonium concentration, did not produce this effect when added to Aminosol. Also, a prompt venous blood NH_4-N rise did not occur in this patient during a slow-rate infusion containing l-glutamic acid, l-aspartic acid and NH_4Cl in concentrations approximating those in Aminosol. These observations suggest that Aminosol, in spite of its high concentration of ammonium-nitrogen, did not produce prompt venous blood ammonium increases when infused slowly because of an in vivo ammonium-neutralizing effect of the glutamic, and possibly aspartic, acids it contained.

Control of Blood Ammonia in Cirrhosis by Oral Neomycin

By *Curtis J. Fisher and William W. Faloon.* Department of Medicine, State University of New York, Upstate Medical Center, Syracuse, New York.

Ammonia formation by bacterial action upon nitrogenous compounds in the intestine has been incriminated in the blood ammonia elevation associated with hepatic coma. Alterations in blood ammonia following changes in intestinal flora during oral Neomycin have been studied in 8 cirrhotic patients, 2 of whom had episodic stupor.

Six patients without neurologic signs received high protein diets, and postprandial venous ammonia was determined 3 times weekly during 7-day periods of: (1) control, (2) 12 Gm. Neomycin/day by mouth, (3) postNeomycin. Marked reduction in ammonia concentration occurred within 48 hours of beginning Neomycin in 5 patients, and at 96 hours in the sixth. The average blood ammonia during Neomycin administration was 34% of control levels (range 17–44%). Antibiotic withdrawal was followed by a rise in blood ammonia in 48 hours, and the average level during the third period was 71% of the control (range 48–113%).

Stool cultures were obtained from 2 patients, both of whom had a normal flora prior to Neomycin therapy. During Neomycin administration no bacterial growth was obtained, although yeast were cultured which showed no urease activity. In 1 patient, culture during the postNeomycin period showed a return to normal flora. Diarrhea occurred in 4 of the patients but had no demonstrable effect upon the degree of blood ammonia reduction.

In 2 patients with episodic stupor, Neomycin resulted in marked reduction in blood ammonia beginning within 24 hours. One patient, in whom 35 Gm. protein/day previously induced coma, was able to tolerate 90 Gm./day while receiving Neomycin. Cessation of the antibiotic resulted in coma on 2 occasions. Ammonium chloride administration, however, induced coma despite Neomycin administration.

These observations suggest that Neomycin effectively reduces venous blood ammonia levels by altering the intestinal bacterial flora.

The Blood "Ammonia" Following Portacaval Shunts in Cirrhosis of the Liver

By *Thomas C. Chalmers, Carl W. Hughes and Frank L. Iber.* Walter Reed Army Institute of Research, Washington, D. C. and the Lamuel Shattuck Hospital, Boston.

In an effort to define the contribution of portacaval shunting of blood to elevation of the blood "ammonia" concentration in hepatic failure, 12 patients with cirrhosis were studied before and after surgery for portal hypertension. Two had splenorenal shunts and 10 had end-to-side portacaval anastomoses.

During the weeks before operation the mean blood "ammonia" level was 1.20 γ/ml., and the means for the first and second postoperative weeks were 1.58 and 1.15 γ/ml. respectively. The peak level occurred on the first or second postoperative day. The mean rise following operation was $0.38 \pm .10$ γ/ml. ($p < .01$). Frequent measurements in 1 patient during operation revealed a sharp rise within 7 minutes of the opening of the shunt, followed by a fall to the preshunt level by the end of the operation. There was a second rise 24–48 hours after operation with a return to normal by the fifth postoperative day. Similar observations in 3 additional patients with cirrhosis who had major abdominal operations did not show any rise in blood "ammonia."

Two of the shunted patients, with marked portal hypertension and relatively good liver function, were fed high protein diets (3 Gm. protein/Kg.) for periods of 2–3 weeks before and again 3 months after operation. The mean blood "ammonia" concentration was slightly higher during the postoperative period, but the difference was significant in only 1 patient.

It is concluded that after the postoperative period of impaired liver function, the body adequately compensates for the added "ammonia load" brought about by complete diversion of portal blood from the liver. Hepatocellular failure would therefore seem to be the principal cause of the elevated blood "ammonia" almost always found in patients with terminal liver disease.

Peripheral Blood Flow in Patients with Cirrhosis of the Liver at Rest and during Exercise

By *Walter H. Abelmann and J. Morrison Hutcheson, Jr.* Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Depart-

ment of Medicine, Harvard Medical School, Boston. (Aided by a grant from the Massachusetts Heart Association.)

In order to assess further the nature of the high cardiac output state encountered in patients with cirrhosis of the liver, peripheral blood flow was estimated by means of whole leg venous occlusion air plethysmography at rest and during mild rhythmic leg exercise in the postabsorptive state. Patients with evidence of heart disease, acute blood loss, thiamine deficiency, anxiety, hematocrit below 30%, and more than minimal ascites or edema were excluded.

Resting leg blood flow was found to be 1.4 ± 0.5 cc./100 Gm. leg/min. (mean ± s.d. of sample) in 19 normal subjects and 3.6 ± 0.6 cc./100 Gm./min. in 20 patients with moderate to advanced Laennec's cirrhosis. The difference between the 2 means is significant ($p < 0.01$). In 6 (30%) of the cirrhotics resting leg blood flow exceeded the upper limit of normal (mean + 2 s.d.). In 3 of these 6 patients cardiac output was determined by right heart catheterization and was found to be elevated in 2. In the group studied, increased resting peripheral blood flow appeared to be independent of fluid retention, jaundice, anemia and treatment with thiamine.

During mild leg exercise, maximum leg blood flow was 3.6 ± 0.6 cc./100 Gm./min. in 13 normal subjects and 6.7 ± 6.5 cc./100 Gm./min. in 19 cirrhotic patients. The difference between these means is significant ($p < 0.05$). Eleven of the cirrhotic patients exceeded the mean + 2 s.d. of the control group.

The data suggest that the high cardiac output state in cirrhosis is accompanied by increased peripheral blood flow both at rest and during exercise. The magnitude of the blood flow at rest and the excessive increase during exercise suggest that the vascular bed of skeletal muscle plays a major role in the high output state of patients with cirrhosis.

Thickening and Contraction of the Palmar Fascia (Dupuytren's Contracture) Associated with Alcoholism and Hepatic Cirrhosis

By *Stanley J. Wolfe, William H. Summerskill and Charles S. Davidson.* Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

A study was undertaken to verify an earlier clinical impression that Dupuytren's contracture occurs frequently in alcoholics with hepatic cirrhosis treated at Boston City Hospital.

Three groups were examined for palmar contraction: 57 (35 male, 22 female) alcoholics with hepatic cirrhosis; 55 (49 male, 6 female) alcoholics without clinically evident liver disease; and 53 (34 male, 19 female) nonalcoholics without liver disease, serving as controls. All were patients seen consecutively on wards and in the clinics of the Boston City and Long Island Hospitals. In addition, records were reviewed to determine the incidence of Dupuytren's contracture in 158 alcoholics with hepatic cirrhosis studied in the 8-year period 1946–54 in the Thorndike Memorial Laboratory.

In males, the deformity occurred in 66% of the alcoholics with cirrhosis, in 27% of the alcoholics without liver disease, and in 12% of the controls. The review of previous records revealed an incidence of 42% in male alcoholics with cirrhosis. Results in females tended to support those in males but were based on fewer observations.

These data support the impression that male alcoholics with cirrhosis are more likely to have palmar contractures than are male nonalcoholics in this hospital and in other hospital populations reported in the literature. The alcoholics without liver disease had a greater incidence of contracture than controls, but less than those alcoholics with cirrhosis.

The absence of a study designed to show the incidence of alcoholism and cirrhosis in patients presenting with Dupuytren's contracture, the method of selection of groups and the possible and unresolved influence of hereditary and ethnic factors prevent further conclusions. On the basis of our findings, however, it is suggested that factors predisposing to hepatic disease in the alcoholic may also contribute to the development of Dupuytren's contracture.

A Major Defect in Protein Metabolism in Hepatolenticular Degeneration

By *Frank L. Iber, Thomas C. Chalmers and L. Lahut Uzman.* Walter Reed Army Hospital, Washington, D. C.

The urinary excretion of amino acids and copper during different dietary intakes was investigated in an asymptomatic 12-year-old boy with hepatolenticular degeneration. The excretion of these substances did not change significantly following the oral administration of 15 Gm. individual amino acids An immediate increase in excretion of α-amino acid nitrogen and copper occurred when the dietary intake of protein was changed from 10 to 100 Gm./day. On the first day of high protein intake the excretion of amino acid nitrogen was as much as 32% of total urinary nitrogen, diminishing rapidly to control values by the third day. The excretion of copper paralleled that of amino acids. The addition to the *low* protein diet of 110 Gm. purified casein produced an increase of urinary amino acid nitrogen equivalent to 8% of the ingested casein and a 100% increase of urinary copper. The addition to the *low* protein diet of pure l-amino acids identical with those contained in 110 Gm. purified casein did not produce an increase in excretion of either amino acid

nitrogen or copper. That the patient was still capable of the original response was demonstrated when the high protein diet was reinstituted. Repeated changes from low to high protein diet produced comparable increases in aminoaciduria, but the excretion of copper, initially excessive, decreased progressively on successive dietary changes. This suggests that the body stores of copper are not all labile in hepatolenticular degeneration. Urinary polypeptides were demonstrated chromatographically before and during the administration of casein and the amino acid mixture, and the quantity detected was similar, whether copper excretion was high or low.

An abrupt increase in the dietary intake of whole protein produced an intense, transient outpouring of amino acids and copper in the urine, whereas increased intake of amino acids had no effect.

NERVOUS SYSTEM AND MUSCLE

The Urinary Excretion of 5-Hydroxy-3-Indoleacetic Acid (HIAA) in Patients with Schizophrenia and in Control Subjects

By *Eli Robins, Irene P. Lowe and Nilda M. Havner.* Department of Psychiatry and Neurology, Washington University School of Medicine, St. Louis.

Recent work has indicated that serotonin may have a role in brain function. There has also been a suggestion that abnormalities in serotonin metabolism may be implicated in schizophrenia. In this study, the urinary excretion of HIAA (a major metabolite of serotonin) was measured in 33 schizophrenic patients (22 men and 11 women), 17 psychiatrically ill controls (7 men and 10 women, who were suffering from manic-depressive psychosis, psychopathic personality, anxiety neurosis or obsessive compulsive neurosis), and 18 well controls (9 men and 9 women, hospital personnel). Morning urine samples were collected and analyzed for HIAA and creatinine. The compound which was measured in urine was identified as HIAA by comparison with an authentic sample of HIAA with regard to its chromatographic behavior, absorption spectrum and distribution between solvents. Results are expressed as μg. HIAA/mg. creatinine in the urine sample. There were no significant differences in this ratio related to age within each of the groups. Women, however, had a significantly higher ratio than did men in the schizophrenic group and in the well controls (presumably because women excrete less creatinine than men and the daily excretion of HIAA is more nearly equal in the 2 sexes). The values ± s.e.m. were: for men, schizophrenic, 2.16 ± 0.16; psychiatrically ill controls, 2.67 ± 0.26; well controls, 2.09 ± 0.10; and for women, schizophrenic, 3.21 ± 0.30; psychiatrically ill controls, 3.42 ± 0.37; well controls, 3.15 ± 0.36. There were no statistically significant differences between schizophrenics and well controls, between schizophrenics and psychiatrically ill controls, and between psychiatrically ill controls and well controls. Since only a small percentage of total body serotonin occurs in brain, abnormalities in its metabolism or storage in brain would not necessarily be reflected in the excretion of HIAA. However, these results do indicate that there is no abnormality of serotonin metabolism in these psychiatric diseases, as reflected in the urinary excretion of a major metabolite.

The Failure of Organic Phosphates to account for the Preservation of Tonicity in Potassium Deficient Rat Muscle

By *Robert Schwartz.* Children's Hospital, Boston

In experimental potassium deficiency, the loss of muscle cellular potassium is usually only partially replaced by sodium. Since plasma sodium concentration remains at a normal level, tonicity of the cells must be preserved by change in anions or nonelectrolyte. In order to determine whether organic phosphates participate in such a phenomenon, muscle from potassium deficient rats was analyzed for several of the organic phosphates according to the technics of Umbreit et al.

A hind limb of the K-deficient anesthetized animal was frozen in situ, then, following exsanguination via aorta, the muscle of the opposite limb was removed for electrolyte analysis. Weighed samples of frozen muscle were extracted with cold trichloracetic acid and subsequently separated into the barium soluble and insoluble fractions as well as the barium soluble, alcohol insoluble fraction. Serum and muscle electrolyte analyses indicated the typical hypokalemic, hypochloremic alkalosis with diminished muscle potassium and increased cellular sodium. Serum P was normal. Likewise, total P, inorganic P, creatine P, ATP-ADP 7 min. hydrolyzable P, glucose 1-P, fructose 1, 6-P and fructose 1-P were normal. Muscle glycogen and the pentose of barium insoluble fractions (ATP-ADP) were unchanged.

The data suggest that an increase in osmotically active organic phosphate in the muscle with diminished potassium content is unlikely, even though a decrease in cellular pH (from hydrogen-potassium exchange) may have occurred.

Although no net change in the concentration of glycogen and the other measured components of the glycolytic system was observed, no conclusions can be drawn regarding the effect of potassium on

glycolysis in muscle, since no rate measurements were made.

Muscle Composition in States of Abnormal Plasma Sodium Concentration

By *James W. Agna and Harvey C. Knowles, Jr.* Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati.

There is evidence suggesting that alterations in plasma sodium concentrations are accompaned by changes in water and electrolyte content of the erythrocyte. These latter changes are believed to be osmoregulatory in nature. Studies have been made on muscle composition to determine if changes therein also occur in the presence of abnormal plasma sodium concentrations.

Analyses have been made of water, fat, nitrogen, chloride, sodium and potassium content of muscle obtained by biopsy from 10 normal subjects, 6 patients with adaption of hyponatremia (unresponsive to salt therapy), 1 patient with depletion hyponatremia (responsive to salt therapy), and 2 patients with hypernatremia. The relations of plasma sodium concentration and the sodium and potassium content of cell or whole tissue expressed per water were significant. In the presence of hyponatremia cellular hypotonicity resulted from a loss of cell potassium with insignificant change in water and sodium content. In 1 patient with hypernatremia, cellular hypertonicity was characterized by a gain in sodium, while in the other, water loss in excess of potassium caused hypertonicity.

These findings suggest that changes in tonicity in extra- and intracellular phases in muscle are interdependent. They also suggest that in adaption hyponatremia, cellular hypotonicity and potassium deficit may be partially responsible for the lowered plasma sodium concentration.

The Nature of Cation Accumulation by Muscle Cells: The Displacement of Potassium by Rubidium and Cesium

By *Arnold S. Relman, Anne T. Lambie, Arlene M. Roy and Belton A. Burrows.* Evans Memorial Hospital, Boston.

Rubidium and cesium, univalent alkali-earth ions with physicochemical behavior similar to that of potassium, penetrate cells readily and can substitute for potassium in many physiologic processes. Current theory explains accumulation of potassium in muscle cells as a passive diffusion along electrochemical gradients maintained by the active extrusion of sodium. Accordingly, the equilibrium muscle/plasma concentration ratios for rubidium and cesium should be equal to that for potassium.

To test this hypothesis, 20 mEq./L. potassium chloride and 20 mEq./L. rubidium or cesium chloride were added to the drinking water of potassium-depleted young rats for a period of 2 or 3 weeks. Up to ⅔ of the normal cellular potassium was replaced by rubidium or cesium, with no change in the total measured cation and only slight reduction in calculated intracellular water. At 2 weeks, mean plasma concentrations (mEq./L.) in the rubidium animals were: K, 1.95 ± 0.36; Rb, 0.8 ± 0.5; Na, 141.4 ± 5.2; muscle concentrations (mEq./L. intracellular water) were: K, 75.4 ± 11.7; Rb, 90.7 ± 11.8; Na, 4.2 ± 2.6. There was no further change at 3 weeks. In the cesium animals at 2 weeks, mean plasma concentrations were: K, 2.0 ± 0.6; Cs, 0.5 ± 0.1; Na, 146.2 ± 3.5; muscle concentrations were: K, 74.5 ± 14.6; Cs, 94.1 ± 11.6; Na, 10.4 ± 4.5. The average muscle/plasma ratio for potassium remained normal in all experiments (about 40), whereas the ratio for rubidium was approximately 115, and that for cesium, 216.

Growing muscle cells thus appear to accumulate these ions at equilibrium in a definite order of preference: Cs > Rb > K. This argues against accumulation by passive diffusion, and instead suggests either: (a) an active inward transport system for which these ions compete, or (b) selective intracellular binding of cation with relatively little change in cellular osmotic activity

RESPIRATORY SYSTEM

The Acute Effects of Inflation of a Pneumatic Suit upon Pulmonary Diffusing Capacity in Normal Subjects

By *B. M. Lewis, R. E. Forster and E. L. Beckman.* Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, and Aviation Medical Acceleration Laboratory, Naval Air Development Center, Johnsville, and Department of Medicine, Wayne University College of Medicine, Detroit.

Application of 75 mm. Hg pressure to the lower half of the body by means of an individually fitted pneumatic (antigravity) suit has been shown to increase the right atrial, pulmonary artery, pulmonary wedge and peripheral artery pressures by 20 to 30 mm. Hg within 5 sec. of full inflation in normal men. We expected that a pulmonary hypertension of this magnitude would distend the pulmonary capillaries and increase pulmonary diffusing capacity for CO (D_L). D_L was measured at an alveolar O_2 tension of approximately 100 mm. Hg by a modification of the Krogh breath-holding technic, using the dilution of inspired helium to calculate the initial alveolar CO concentration. In 3 healthy men there was no significant increase in D_L 20 to 30 sec. after inflation of

the pneumatic suit. However, residual volume, which is needed to calculate D_L, may change during suit inflation because of gas "trapping" in some alveoli as suggested by the following. (1) Functional residual capacity (FRC) prior to suit inflation was greater than the sum of FRC with the suit inflated plus the gas volume expelled during inflation. (2) If, with the suit inflated, the subject washed out most of the N_2 in his lungs by breathing approximately 100% O_2, deflation of the suit produced a sudden increase in expired alveolar N_2 concentration. Even allowing for such changes in residual volume, suit inflation did not significantly increase D_L.

Effect of Mild, Steady-State Exercise on Pulmonary Vascular Resistance of Normal Subjects and Those with Compensated and Decompensated Aortic Valvular Lesions

By *Salvatore M. Sancetta and Jerome Kleinerman.* Departments of Medicine and Pathology, Western Reserve University at City Hospital, Cleveland.

The effect of mild, steady-state exercise (110 to 135 foot pounds/min.) has been investigated in 9 normal subjects and in 18 with pure aortic insufficiency or stenosis, employing the supine position against a variable resistance bicycle ergometer. The 9 normal subjects (group 1) and 5 subjects with aortic valvular lesions (group 2) had resting wedge pressures less than 10 mm. Hg; 11 subjects (group 3) had wedge pressures above 12 mm. Hg.

Mild steady-state exercise produced a fall in pulmonary vascular resistance (PVR) and only slight increases in pulmonary artery pressure (P_{PA}) when the wedge pressure (WP) was less than 10 mm. Hg; there was an increase in PVR and marked increases in P_{PA} when the WP was more than 12 mm. Hg. The significant difference in response of patients with normal, as against those with elevated WP, lends some support to the use of this measurement as an index of cardiodynamic left ventricular competency or failure at rest when dealing with groups of patients with isolated aortic valvular lesions.

The Anatomic and Physiologic Respiratory Dead Space during Rest and Exercise in Patients with Pulmonary Emphysema

By *R. S. Meador, D. O. Shields, B. E. Jay, Russell H. Wilson and Robert S. Evans.* Dallas and Minneapolis.

In patients with pulmonary emphysema, Fry found an increased resistance to flow of air in the bronchioles with a change in the elastic properties of the lung for a given degree of inflation. It is here postulated that the bronchioles in the emphysematous lung may not only collapse during expiration but may be distorted and have a smaller volume than the normal airway during inspiration because of air-trapping and overdistention of large abnormal pulmonary air sacs and bullae. The effect of exercise and hyperventilation on pulmonary physiologic dead space in this disease has not been clearly delineated in contradistinction to that on anatomic dead space.

Method: The volume of the anatomic dead space was estimated with the nitrogen meter. A new method of analysis of the nitrogen meter single breath curve was designed to eliminate the effects of the nonuniform composition of alveolar air in the calculation of anatomic dead space. This was done by locating the inflection point on the single breath expirator curve of the nitrogen meter by taking its first and second derivative. Volume-flow was measured with the pneumotachograph.

The mean anatomic dead space in 18 patients with pulmonary emphysema was decreased from 189.7 to 187.8 ml., and physiologic dead space was increased from 324.8 to 443.0 ml. during exercise.

In patients with severe pulmonary emphysema ventilation of hyperventilated alveoli is increased during exercise, thus the physiologic dead space is greater in magnitude. Anatomic dead space remains the same or is decreased.

Effects of Smoking on Respiratory Mechanics in Chronic Pulmonary Emphysema

By *Robert H. Eich, Robert Gilbert and J. Howland Auchincloss, Jr.* Department of Medicine, State University of New York, Upstate Medical Center, Syracuse.

The acute effects of smoking 1 cigaret on the elastic and nonelastic properties of the bronchopulmonary system were studied in 15 patients with chronic obstructive pulmonary emphysema, in 3 patients with chronic bronchitis, 2 asthmatics without emphysema and 4 normal subjects. For this purpose the esophageal balloon technic with pneumotachometer and integrator was employed. In 8 of the emphysematous patients and the 4 normal subjects duplicate control studies 10 minutes apart were also done to measure the reproducibility of lung compliance and airway resistance; for compliance the second values varied as much as −0.13 to +0.50 L./cm. H_2O from the first, with a mean change of +0.09. Similar changes in the control values for nonelastic resistance were −1.4 to +1.2 cm. H_2O/L./sec., with a mean change of +0.08.

Following the smoking of 1 cigaret (which resulted in cough in only a few subjects) nonelastic resistance in 12 of the 15 emphysematous patients increased more than 1.5 cm. H_2O/L./sec., with a significant mean increase for the group of 2.0 ($p < .01$). These changes did not occur in the nonemphysematous control groups, nor were there significant changes in compliance in either the emphysematous or control groups.

These studies corroborate the clinical impression that emphysematous subjects are especially vulnerable to bronchial irritants, and that smoking

tends to aggravate the increase in airway resistance so characteristic of this disease.

Venous-Arterial Admixture in Polycythemia and Pulmonary Emphysema

By *James P. Lillehei, Robert L. Johnson, Jr., Nancy Wu, E. Richard Halden and Carleton B. Chapman.* Cardiopulmonary Laboratory, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas.

Alveolar-arterial O_2 gradients were determined in subjects breathing pure O_2 at rest. Arterial CO_2 tensions were obtained from pH and CO_2 content and/or by the syringe method of Riley et al. O_2 tension was measured polarographically in plasma. Corresponding mean alveolar O_2 tensions were calculated by the alveolar equation.

The mean alveolar-arterial O_2 gradient of 12 normal subjects after breathing pure O_2 for at least 30 minutes was 43 mm. Hg, with a maximum of 88 mm. Hg. Four patients with polycythemia, proved by the Cr^{51} method, including 2 secondary to pulmonary emphysema (desaturated on 21% O_2) and 2 without detectable cause (normally saturated on 21% O_2), had increased gradients of 277, 159, 367 and 129, respectively. Following reduction of their blood counts with phlebotomies and P^{32}, these gradients were reduced to 100, 105, 158 and 77, respectively. Gradients determined in like manner in 7 patients with chronic bronchopulmonary disease and severe pulmonary emphysema without polycythemia were in the normal range (mean of 53, and maximum of 118).

In conclusion: alveolar-arterial gradients during pure O_2 breathing were found to be similar in normal subjects and in patients with chronic bronchopulmonary disease and pulmonary emphysema without polycythemia. The increased amount of venous-arterial admixture evidenced by elevated gradients in polycythemic patients can apparently be diminished by reducing the red cell mass.

The Effect of Salicylates upon the Ventilatory Response to Carbon Dioxide in Patients with Pulmonary Emphysema and Hypercapnia

By *Philip Samet, Anna Rosenthal and William Bernstein.* Cardio-Pulmonary Laboratory, Mount Sinai Hospital of Greater Miami and the Departments of Medicine and Physiology, University of Miami School of Medicine.

The depressed ventilatory response to inhaled CO_2 in patients with pulmonary emphysema and CO_2 retention has been well documented. The present study was designed to determine whether this abnormal response could be modified by salicylate or salicylate plus Diamox administration. Five patients with hypercapnia were studied. Control measurements of minute ventilation, oxygen consumption, respiratory quotient, alveolar ventilation, and arterial oxygen saturation, pH and CO_2 tension were made at rest and while breathing 3% CO_2 and 5% CO_2 in ambient air. These studies were repeated in all subjects after short-term (less than 1 day) oral salicylate administration. In 3 subjects, similar measurements were made after 1 week of oral salicylates and after 1 week of salicylate and Diamox ingestion. Observations were also made on the effect of salicylate administration of the ventilatory depression following administration of high oxygen mixtures in 4 of the 5 patients with hypercapnia. In all, 24 sets of observations were performed in 5 subjects. The plasma sodium salicylate levels ranged from 10–30 mg. %.

Salicylate ingestion, in any of the 3 previously outlined schedules, resulted in increased levels of ventilation on ambient air and 3 and 5% CO_2 in ambient air. However, the percentage increase of minute and alveolar ventilation on the CO_2 mixtures did not increase. In other words, salicylate administration led to higher levels of ventilation but the sensitivity of the respiratory center to inhaled CO_2 did not increase. Furthermore, the respiratory depression and acute respiratory acidosis subsequent to high oxygen breathing were not prevented by salicylates. Arterial blood CO_2 tension, saturation and pH, and the respiratory quotient were not affected by salicylates. Oxygen consumption and CO_2 production rose somewhat.

These data indicate that respiratory center sensitivity to CO_2 inhalation, in patients with pulmonary emphysema and hypercapnia, is not increased by salicylate administration.

The Effect of Salicylate on the Respiratory Response to Carbon Dioxide in Patients with Chronic Respiratory Acidosis

By *Daniel S. Lukas and Thomas Killip, III.* Cardio-Pulmonary Laboratory and Department of Medicine, New York Hospital-Cornell Medical Center, New York City. (Aided by a grant from the National Heart Institute.)

Recently published investigations have demonstrated that the respiratory response to CO_2 breathing in normal man is increased after the administration of salicylate. This effect appears to be related to enhanced sensitivity of the respiratory center. Similar data regarding the effect of salicylate on sensitivity to CO_2 in patients with chronic respiratory acidosis are not available.

The response of 3 patients with pulmonary emphysema and chronic hypercapnia to the breathing of 5% CO_2 in air was studied before and after the oral administration of 2.8 Gm. aspirin. Expired and alveolar ventilation and the concentration of the respiratory gases and H^+ ion in the arterial blood were measured. Prior to aspirin the increase in alveolar ventilation per mm. Hg rise in $PaCO_2$ was

markedly subnormal (0.04–0.24 L./min./M.²), as was the increase per billionth mol/L. rise of H^+ ion in the arterial plasma (0.06–0.37 L./min./M.²).

This subnormal response was not modified by aspirin, despite levels of salicylate in the plasma (12.4–18.9 mg.%) previously shown to be associated in the normal with a 2–4-fold augmentation of the response of alveolar ventilation to increase in arterial blood PCO_2 and H^+ ion.

The data provide additional evidence that function of the respiratory center in chronic respiratory acidosis associated with pulmonary disease is seriously disturbed.

Ultrafiltrable Calcium in Hyperventilation Tetany and Respiratory Acidosis Produced Experimentally in Dogs

By *Ananda S. Prasad, E. B. Brown, Jr. and E. B. Flink.* Departments of Medicine and Physiology, University of Minnesota and V. A. Hospital, Minneapolis, Minn.

Tetany in hyperventilation has been ascribed to a sufficiently great decrease in ionic calcium, but this has not been proved experimentally. These experiments were carried out to study the status of ultrafiltrable calcium in hyperventilation tetany and respiratory acidosis.

Femoral artery blood samples were collected under oil from dogs anesthetized with sodium Pentothal. Samples were obtained before, during and following 30 minutes of hyperventilation produced by a positive pressure respirator, or 30 minutes of breathing 30% CO_2 in oxygen.

The plasma was separated under oil, and pH was controlled by handling it inside a plastic tent ballooned up with proper CO_2 and O_2 mixtures. Ultrafiltrate of plasma was obtained by using a standard centrifuge, as previously described. The ultrafiltrable calcium during hyperventilation tetany showed no appreciable change from the initial sample. However, the ultrafiltrable calcium during the recovery period showed a marked rise, the total calcium remaining unchanged.

The ultrafiltrable calcium during respiratory acidosis showed a slight increase, but during recovery period a marked decrease below the original control value was noted, the total calcium remaining unchanged.

In previous work it was noted that plasma potassium concentration rose during respiratory acidosis in dogs, and increased further when the dogs were returned to air breathing. The heart shows severe arrhythmias, and ventricular fibrillation often occurs during the first few minutes after return to air breathing. It seems likely that the simultaneous reduction in plasma ionic calcium and the rise in plasma potassium concentration at this time are responsible for these cardiac effects.

Hemodynamic Studies in the Pulmonary and Peripheral Circulation during Acute Hypoventilation

By *A. Buhlmann, G. Hoseli and P. Luchsinger.* University Hospital, Zurich, Switzerland

Eight patients without heart or lung disease were studied for pulmonary and cardiac function during acute hypoventilation. The patients were in general anesthesia, and under the influence of curare. Respiration was maintained and controlled by an Engstrom respirator. Data were obtained for the following: brachial and pulmonary artery pressure, cardiac output, O_2 uptake, CO_2 output, arterial and venous blood gas tensions, pH and electrolytes.

During hypoventilation the alveolar ventilation was reduced to 60–70% of the normal for a period of 10–15 min. This caused a respiratory acidosis with the characteristic changes in the arterial blood gases. Along with these changes the pressure increased in the pulmonary and peripheral circulation, but the cardiac output remained about the same and did not show characteristic variations. While hypoventilating with 100% O_2, the pulmonary resistance was somewhat less, compared to the hypoventilation with room air, but the pH decreased even more with the increase of the oxyhemoglobin content in the arterial blood (Bohr effect). After hypoventilation was discontinued, the pressure normalized with the increase in ventilation within 8 to 10 min. Na, K and Cl in the serum did not show any significant change in the experiments.

During hypoventilation of 1 lung and hyperventilation of the other, using 2 respirators, there was no marked increase of the pressure even if there was a slight arterial hypoxemia, as long as the mean alveolar and arterial pCO_2 stayed within normal limits.

These investigations confirm the direct relationship between alveolar gas tension and resistance in the pulmonary circulation, as found in chronic alveolar hypoventilation in emphysema, bronchial asthma, etc.

Mechanics of Respiration in Anesthesia

By *Nancy Wu, William F. Miller and Nellie R. Luhn.* Cardiopulmonary Laboratory, Department of Internal Medicine, and Department of Anesthesiology, University of Texas Southwestern Medical School, Dallas.

In spite of growing interest in the nature of pulmonary mechanics in normal subjects and individuals with pulmonary disorders, little is known of the mechanics of breathing under general anesthesia. For this reason, the present study was undertaken.

Twelve patients with no history of pulmonary disease and normal pulmonary function were studied. All patients were given preoperative opiates and anesthetized with cyclopropane for induction.

Intubation was followed by surgical plane 1–2, ether-oxygen anesthesia. Pulmonary compliance and resistance were measured before and intermittently throughout the anesthetic procedure by simultaneously recording respiratory volume, air flow and transpulmonary pressure. Arterial blood gas and pH determinations, as well as arterial and central venous pressure measurements, were made.

Compliance decreased in every case during anesthesia. The pulmonary viscous resistances were markedly increased in some cases and were not significantly changed in others. Respiratory rate increased (probably due to ether) out of proportion to the slight increase in minute ventilation, and thus tidal volume decreased. This, superimposed on a depressed respiratory center, resulted in rises in arterial pCO_2 during the first 2 hours of anesthesia. With restoration of respiratory center sensitivity, the tidal volume increased and arterial pCO_2 returned to normal, independent of levels of compliance or resistance.

The net result is an increase in the work of breathing, owing to: decreased pulmonary compliance, increased pulmonary airway or tissue viscous resistance, and augmented levels of ventilation.

Decreased compliance probably resulted from: (1) augmented respiratory frequencies in the presence of increased pulmonary resistance; or (2) increased pulmonary blood volume or pulmonary arterial pressure; or (3) decreased ventilatable lung space owing either to the Trendelenburg position or to areas of complete bronchial obstruction.

Increased airway or tissue viscous resistance may be due either to reflex bronchospasm or to partially obstructive secretions.

Alterations in Cerebral Circulation and Function in Cheyne-Stokes Respiration

By *Herbert O. Sieker, Herbert R. Karp and Albert Heyman.* Department of Medicine, Duke University School of Medicine, and the V. A. Hospital, Durham.

The etiology of Cheyne-Stokes respiration and the alterations of consciousness frequently observed with the periodic breathing are poorly understood. Cyclic changes of consciousness and alterations in arterial blood gases, cerebral arteriovenous oxygen differences (A-V O_2), cerebral circulation time (dye curve), cerebrospinal fluid pressure, and the electroencephalogram were correlated during phases of periodic breathing. Repeat observations were made in 8 subjects, either with predominant cerebral vascular disease or congestive heart failure.

At midhyperpnea, the arterial pCO_2 and spinal fluid pressure were increased; oxygen saturation, cerebral circulation time and cerebral A-V O_2 were decreased. Conversely, at midapnea, arterial pCO_2 and spinal fluid pressure were decreased, while arterial oxygen saturation, cerebral circulation time and cerebral A-V O_2 were increased. The changes in arterial blood gas tensions were out of phase with the periodic breathing, particularly in severe heart failure with a prolonged circulation time. The mean cerebral A-V O_2 during apnea was 8.1 vol. % (range 6.6 to 10.6) with an average decreased of 25% in early hyperpnea.

Fluctuations of consciousness with increased awareness during midhyperpnea were noted particularly in patients with heart failure. The electroencephalographic activity correspondingly changed from a high amplitude slow frequency during apnea to low amplitude fast activity during hyperpnea.

During apnea, with more normal arterial blood gas tensions, the cerebral A-V O_2 difference is abnormally wide and is associated with decreased awareness and slow electroencephalographic activity. During hyperpnea, when blood gas tensions are most severely deranged, the cerebral function shows improvement, as manifested by increased awareness and the EEG pattern of arousal. The narrowed cerebral A-V O_2 difference and the increase in cerebrospinal fluid pressure observed are consistent with an increase in cerebral blood flow during hyperpnea. It is suggested from these data that the periodic alteration in CBF is an important factor in the etiology of Cheyne-Stokes respiration and the frequently associated fluctuations in consciousness.

Needle Biopsy of the Parietal Pleura

By *Paul Heller, William F. Kellow and Bernhard Chomet.* Medical Service and the Department of Pathology, West Side V. A. Hospital, Chicago; and the Department of Medicine, University of Illinois College of Medicine.

The utilization of all traditional diagnostic methods in patients with pleural disease frequently fails to yield a diagnosis. The additional help obtained from biopsy of the pleura in such circumstances has recently been emphasized by several investigators, but the means of obtaining such biopsies have involved surgical procedures of some magnitude. Needle biopsy of the parietal pleura is a simple procedure without undue risk.

This report deals with 18 patients with pleural effusion, the cause of which was not completely established at the time of biopsy. A caseating granuloma was found in 5 patients; in only 2 of these patients the cultures of the pleural fluid yielded acid fast organisms 3–6 weeks after biopsy. In 4 patients the biopsy specimen disclosed malignant disease; in 3 of these patients it was possible to make a structural diagnosis of mesothelioma, lymphosarcoma, anaplastic carcinoma. In 8 patients the histologic diagnosis of the pleural biopsy was nonspecific fibrosis. This was confirmed in 2 patients at autopsy; 1 patient had a bronchogenic carcinoma, and in the

remaining patients good explanations of their transient pleural effusion were available. They are being followed closely.

This diagnostic procedure has proved helpful in the differential diagnosis of pleural effusion occurring in patients with lymphoma. Except for an episode of bleeding into the pleural space, no complication was encountered.

Serum Glutamic Oxalacetic Transaminase (GOT) in Pulmonary Embolization

By *Bernard H. Ostrow, George N. Polis and John M. Evans.* Department of Medicine, The George Washington University Hospital, The George Washington University School of Medicine, Washington, D. C.

Glassner and associates observed normal serum GOT in animals following experimental pulmonary infarction, with GOT determined at 2, 15, 20 and 40 hours postinfarction. In man, on the contrary, we have found elevated serum GOT in approximately one-half of the patients with pulmonary embolization.

Fifteen patients were included in this study, on the basis of acute chest pain, dyspnea and, frequently, syncope and cyanosis. Four had an acute cor pulmonale pattern and 10 acute atrial arrhythmias, by electrocardiogram. In 3, icterus appeared on the fourth postembolization day, 5 had x-ray evidence of pulmonary infarction and 5 had hemoptysis.

In 7 of the 15, GOT (by the method of Karmen, Wroblewski and LaDue) was normal, averaging 30 U/ml. The other 8 had elevated values averaging 62 U/ml. Elevated GOT correlated best with x-ray evidence of pulmonary infarction, 4 of the 5 patients having increased GOT. In 7 of the 8 positive cases, the peak rise appeared on the third to sixth day after embolization, while the mean peak was reached on the fourth day and averaged 79 U/ml.

In contrast to acute myocardial infarction, where the mean peak GOT increase occurs at 26 hours from onset, the peak level in pulmonary embolization did not appear until the fourth day and the levels were much lower. The delayed rise of GOT frequently was associated with the development of jaundice. GOT elevation in pulmonary embolization may be due to pulmonary necrosis, hemolysis, hepatic impairment or interplay of these factors.

It is concluded that pulmonary embolization with infarction may be associated with a moderate rise in serum GOT appearing later than the increase seen in acute myocardial infarction.

RHEUMATIC STATES

Influence of Age on Recovery of β Hemolytic Streptococci: Relation to Rheumatic Fever

By *Murray M. Streitfeld and Milton S. Saslaw.* Department of Medical Research, National Children's Cardiac Hospital, and University of Miami Medical School, Miami, Florida.

Age appears to play a definite role in influencing the percentage of people harboring group A β hemolytic streptococci. This variation in streptococcal rate may indicate a significant effect on the frequency of rheumatic fever at various ages.

Throat cultures were taken monthly from 4 categories of presumably healthy individuals in Miami, Florida, over a 4-month period: (1) 100 children per month, ages 6–9; (2) 100 children per month, ages 12–15; (3) 100 adults per month, drawn from people living in this area; and (4) a group of adults sent from cities throughout the United States to Miami for physical examination for an airline company.

Group A β hemolytic streptococci were recovered from the throat cultures in the following percentages: (1) elementary school children, 9–16% per month (av. 12.5%); (2) junior high school children, 4–9% (av. 6%); (3) local adults, 1–3% (av. 2%); (4) transient adults, 0–2.5% (av. 1.9%).

Previous studies at the National Children's Cardiac Hospital on 7600 throat cultures taken from elementary school children had established an average monthly recovery rate of 14.2%, corresponding to the present rate of 12.5% in the same age range.

Groups B, C, F and G β hemolytic streptococci were recovered frequently; the over-all percentage of nongroup A β streptococci also decreased with increasing age. This decrease in isolation rate was not as marked as with group A organisms.

These findings are important in that they demonstrate definite variation of recovery rate of group A organisms, % isolated decreasing markedly with increasing age. The rate in adults, at least, did not show any effect of geographic origin insofar as could be determined on cultures taken in Miami.

It can be seen that young children (age 6–9) in this investigation had twice as many group A organisms as older children (age 12–15) and 6 times as many as adults. The variation in the ratio of frequency of isolation to age parallels the known distribution curve of occurrence of rheumatic fever at different ages.

The Effect of Salicylates and Adrenocortical Hormones on C-Reactive Protein

By *Elmer Pader, Arthur J. Lewis and Samuel K. Elster.* Department of Medicine, the Mount Sinai Hospital, and the New York University Research Service, Goldwater Memorial Hospital, Welfare Island, New York.

The determination of C-reactive protein has found wide application as a sensitive index of activity in the management of acute rheumatic fever. As the acute inflammatory manifestations of rheumatic fever are suppressed by salicylates and/or adrenocortical hormones, C-reactive protein disappears from the blood. The present study was undertaken to determine whether these drugs cause disappearance of C-reactive protein by a nonspecific effect on the protein or by suppression of the inflammatory process responsible for its formation.

Patients with noninflammatory disease (metastatic carcinoma) were selected who had large amounts of C-reactive protein in the blood. After a suitable control period, 5 patients received 2.4 to 4.8 Gm. aspirin orally, 2 patients each received 100–150 mg. cortisone orally, 80 U corticotropin gel intramuscularly and 80 mg. prednisone orally daily for periods of at least 2 weeks. Blood samples were taken 3 times weekly, prior to and during the administration of these drugs. The samples were analysed for C-reactive protein content, utilizing a microprecipitin technic with C-reactive protein rabbit antiserum. In no case was the amount of C-reactive protein reduced.

It is inferred that the disappearance of C-reactive protein from the blood of patients with acute rheumatic fever treated with salicylates or adrenocortical hormones is due to suppression of the inflammatory process rather than to a nonspecific effect on the C-reactive protein itself.

Enquiry into Causes of Lowered Spinal Fluid Sugar Content: In Vivo and In Vitro Observations

By *Aldona Baltch and Winifred Osborne.* Department of Medicine, State University of New York, Upstate Medical Center and University Hospital, Syracuse, New York. (Aided by a grant from the Bristol Laboratories.)

This study is designed to determine whether or not infecting microorganisms alone are responsible for the usual low spinal fluid sugar content in bacterial meningitis.

In vitro observations: Sugar content of sterile cell-free human spinal fluid does not change at incubator, refrigerator, or freezing temperatures. When bacteria are added to similar spinal fluid and incubated for 24 hours, concentration of sugar therein falls significantly. The major drop occurs after the 18th hour. Pneumococci, staphylococci and β hemolytic streptococci are equally capable of reducing sugar level. Reduction is from 50 to 90%. Under conditions of the study, meningococcus could not be grown.

In vivo observations: Sterile irritative meningitis is produced in rhesus monkeys and dogs by intracisternal administration of either agar or streptokinase-dornase suspension. Resulting pleocytosis is variable, ranging from 60 to 13,000 white blood cells per mm.^{3} Regardless of the degree of pleocytosis, in vivo, drops in sugar content are not observed at 24 and 48 hours. A significant fall, >50%, in sugar content occurs in sterile spinal fluid with more than 2000 cells per mm.^{3} upon incubation in vitro for 24 hours. Little or no fall is seen in spinal fluids with less than 600 cells per mm.^{3} when incubated. When streptokinase-streptodornase is added to sterile spinal fluid in vitro, no significant drop in the spinal fluid sugar occurs.

Data warrant the following conclusions: (1) Microorganisms certainly are capable of utilizing rapidly sugar content of spinal fluid in vitro. They are also capable of glycolysis in patients with meningitis. (2) Polymorphonuclear leukocytes can similarly cause appreciable reduction in spinal fluid sugar content in vitro, when there is a marked pleocytosis. Cells do not alone produce, in vivo, a drop in sugar level. It would appear that the speed of glycolysis by white cells is slow enough in vivo that, with continuing replenishment from body stores, reduction is practically not observed.

Sequelae of Prednisone Treatment of Acute Rheumatic Fever

By *Richard T. Smith and Robert A. Good.* Pediatric Research Laboratories of the Variety Club Heart Hospital and the Department of Pediatrics of the University of Minnesota Medical School, Minneapolis.

In an experimental attempt to prevent cardiac sequelae, 11 children having acute rheumatic fever were treated with large doses (up to 100 mg./M.^{2}/day) of prednisone for 40 to 171 days. Because of severe osteoporosis and compression fractures of vertebrae in 3 of the patients, the study was discontinued, the dose being reduced step-wise over a 3–4-week period.

During the early post-treatment period, marked and prolonged "rebound," with elevation of the sedimentation rate, appearance of C-reactive protein, fever, but no rheumatic manifestations, occurred in 9 of the patients. In addition, 5 of these children developed a peculiar syndrome lasting 4–14 days, characterized by intense pruritus and painful erythema nodosum-like lesions of the skin; and 2 developed extensive panniculitis. Biopsy material from the involved areas revealed perivascular inflammatory reaction, with fibrinoid occlusion of multiple venules, and striking subcutaneous fat necrosis.

Two children developed congestive heart failure 25 and 60 days after cessation of therapy without

clinical evidence of recurrent rheumatic fever. One of these children expired; at autopsy no evidence of recrudescent rheumatic carditis was evident, but fat necrosis and multiple vascular lesions, similar to those seen in the skin biopsy specimens, were prominent. Clinical, photographic and histopathologic data on these patients were gathered. Similar clinical and histopathologic changes occurred in a leukemic patient following prolonged prednisone therapy.

These observations, taken with other available evidence, permit the hypothesis that "rebound" after prolonged steroid therapy may reflect the introduction of a new disease process, probably involving vascular integrity, rather than a recrudescence of previously existing rheumatic fever.

Also, the observations indicate that the multitudinous physiologic and biologic effects of these hormones are still not fully understood, and illustrate the necessity for caution before advocating widespread use of large doses of steroids in treatment of acute rheumatic fever.

Antigenicity of Type-Specific Protein of Group A Streptococci

By *George J. Friou.* V.A. Hospital, West Haven, Connecticut

Injection of heat-killed whole group A streptococci of most strains regularly stimulates production of antibodies against the respective type-specific "M" protein. Extracts made by boiling at an acid pH give precipitin reactions against homologous antisera, but fail to cause antibody formation when injected into rabbits. It is generally considered that the vigorous extraction procedure results in a loss of antigenicity of the type-specific protein. While this may be a partial explanation, another factor of possible importance has not been studied. It is possible that the difference may be due to the soluble condition of the type-specific protein in the extracts, compared with its relatively inaccessible location and resulting slow release from whole organisms.

To test this hypothesis, group A streptococci were extracted by boiling for 10 minutes at an acid pH, and the extract partially refined by precipitation twice with ethanol. An alum precipitated suspension was prepared from ½ of this product. One group of rabbits received intramuscular injections of the solution of refined extract, while others received simultaneous injections of alum precipitate representing an identical volume of solution. There was a marked difference in type-specific antibody response between the 2 groups, indicating that in a particulate, slowly absorbed state, such extracts are active antigens.

The Specific Determination of Chondroitin Sulfate in Adult Urine using Radioactive Chondroitin Sulfate

By *Robert J. Soberman and Alfred A. Smith.* Department of Medicine, New York University College of Medicine, New York City.

Chondroitin sulfate, an anionic polysaccharide, is an important constituent of the ground substance. The latter is thought to play an important role in inflammation and repair, ion storage and transport and structural support. Changes in concentration and excretion of chondroitin sulfate may reflect basic alterations in these functions and may lend insight into the mechanisms involved.

A consideration of the relatively nonspecific methods currently employed for its estimation led to preparation of radioactive chondroitin sulfate for the determination of this substance. The following data are presented in support of the purity and stability of the preparation: (1) no change in specific activity occurred following repeated precipitation and dialysis, (2) specific electrophoretic mobility characteristic of chondroitin sulfate, (3) quantitative recovery from water and urine.

Utilizing radioactive chondroitin sulfate we have been able to determine specifically the chondroitin sulfate content of urine by the determination of the ratio of counts to glucuronic acid, calculating the chondroitin sulfate on the basis of the glucuronic acid content according to the following equation:

$$\frac{G1}{G1 + G2} = \frac{K2}{K1}$$

G1, initial concentration of glucuronic acid; G2, concentration of glucuronic acid of unknown; K1, specific activity of added chondroitin sulfate; K2, final specific activity of chondroitin sulfate.

By this procedure it has been shown that the ratio of the initial to the final specific activity is equal to the weight fraction of the endogenous to the sum of the endogenous and added chondroitin sulfate. Since analysis depends on determination of specific activities, quantitative isolation processes are unnecessary.

The excretion of chondroitin sulfate in adult urine as measured by this procedure has ranged between 1.9 and 5.9 mg./24 hr. This method is being extended to analysis of other body fluids and tissues in normal and pathologic states.

Peptic Ulcer in Rheumatoid Arthritis: The Role of Arthritis Therapy

By *Fred Kern, Jr., Jack G. Lukens and Glen M. Clark.* Department of Medicine, University of Colorado School of Medicine, Denver.

Although it is generally believed that adrenocortical hormones lead to the activation of peptic ulcer, certain inconsistencies in the pertinent laboratory and clinical data directed our attention toward an examination of our clinical experience.

All patients with rheumatoid arthritis currently being treated in the Colorado General Hospi-

tal Arthritis Clinic comprise the patient material of this study. All information pertaining to gastrointestinal symptoms and diagnoses recorded in their charts during the past 10 years was collected and analyzed in relation to drug therapy for arthritis. The median follow-up of this group of 79 women and 42 men is 16 months. Eighty-three patients were treated with salicylates alone for varying periods of time; 69 were treated with phenylbutazone and 90 with adrenal steroids (cortisone, prednisone and Prednisolone). The usual dose of steroids used was small: cortisone, 40–50 mg./day and prednisone 15 mg./day.

There were 13 patients with peptic ulcer. The incidence of ulcer among women was 5 times as great as in the general population. Those patients whose arthritis had been present for at least 10 years had a significantly higher incidence of ulcer than those with arthritis for less than 10 years. A peptic ulcer appeared for the first time in 2 of the 90 patients during treatment with adrenal steroids, 1 of 83 taking salicylates and 5 of 69 taking phenylbutazone. The small doses of cortisone and prednisone used in our patients did not appear to be related to the initiation or exacerbation of peptic ulcer, while the administration of phenylbutazone was attended by a high incidence of ulcer and a large number of complications.

SKIN

Increased Tissue Histamine in Urticaria Pigmentosa: Preliminary Observations on the Site of the Biochemical Error

By *Lytt I. Gardner and Artelissa A. Tice.* Department of Pediatrics, Upstate Medical Center, Satote University of New York, Syracuse.

It has been found in several laboratories that mast cells contain very large concentrations both of histamine and of heparin. The syndrome of urticaria pigmentosa is characterized by generalized hyperplasia of mast cells. We have had the opportunity to study tissue from a boy with urticaria pigmentosa who developed an urticarial rash at age 2 months, and who finally died with intraperitoneal hemorrhage at 5 years.

Trichloracetic acid extracts of liver and spleen were subjected to ascending chromatography on paper, using the n-butanol:acetic acid:water system of Slotta. Histamine was determined by the diazo reagent of Rosenthal and Tabor. Estimation of histamine concentration, in terms of histamine base, revealed approximately 1250 μg./Gm. wet liver, and slightly less in the spleen. Analysis of normal liver tissue revealed only 10 to 12 μg./Gm. wet liver. The chromatographic pattern of the urticaria pigmentosa liver was virtually identical to that obtained by Riley and West in their studies of dog mastocytoma tissue.

Even higher values for histamine were independently obtained on the urticaria pigmentosa liver and spleen tissue by Graham, using the method of Lowry et al. In addition, she found histidine decarboxylase activity in the liver of our patient to be several hundred times the activity measurable in normal human liver (personal communication to the authors).

It is now believed that organic acid heparin is the basophilic material of the mast cell granules, and that histamine is the organic base with which the heparin is associated intracellularly. An explanation for the symptomatology in urticaria pigmentosa would be congenital overproduction or underconsumption of either histamine or heparin. If the congenital biochemical lesion were underconsumption of histamine, a lowered rather than an elevated activity of histidine decarboxylase would be expected. Congenital excess of histidine decarboxylase could exist as the primary defect, but congenital biochemical errors more frequently involve an absence rather than an excess of an enzyme. The evidence to date suggests to us that the primary defect in urticaria pigmentosa is excessive concentration of an intracellular organic acid (heparin?). The increased values for tissue histamine are believed to be a homeostatic compensatory overproduction of this organic base in an attempt to "neutralize" the excessive heparin-like organic acid.

THERAPEUTICS

The Control of Therapeutic Experiments: Biologic Variation Resulting from the Treatment Situation

By *James A. Hagans and Stewart Wolf.* Department of Medicine, University of Oklahoma School of Medicine and V. A. Hospital, Oklahoma City.

In the experiments reported, nausea was induced by the ingestion of syrup of ipecac in 30 normal volunteer subjects; in 21 of them on 2 occasions. The incidence of nausea was 100% in the 51 trials. In 5 additional series of experiments, each of the 30 subjects was given blindly a capsule 2 hours prior to ipecac administration. In 54% of these instances, nausea was either milder or did not occur. Two presumably antiemetic agents had been included among the 5 capsules administered. Had there been no placebos included in the study it would have been concluded that the incidence and severity of nausea had been significantly reduced ($p < .001$). There was an equally significant modi-

fication of nausea among the placebo experiments however (46%, $p < .001$). Thus, although no antiemetic effect could be assigned to the agents, the mere fact of administering an agent was effective in mitigating the nausea. Of special interest, however, is the marked biologic variation which occurred following the administration of the agents. The consistent pattern of nausea in the original untreated control observations was completely destroyed. The variation was intraindividual as well as interindividual, only 3 subjects showing a consistent response to drug A, only 4 to drug B and only 4 to placebo. The total variability of "protection" against nausea, vomiting and salivation among the various treatment groups was from 5 to 57%. Despite the wide and significant variations, no agent provided significantly better "protection" than the placebo. Thus statistically significant variation had been introduced into a previously uniform pattern by "treatment," but without establishing evidence of a specific pharmacodynamic effect.

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